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AN ESTIMATION OF THE RESIDUAL VOLUME OF BLOOD IN THE RIGHT VENTRICLE OF NORMAL AND DISEASED HUMAN HEARTS IN VIVO

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IT IS now generally agreed that under physiological conditions the heart is not completely emptied of blood at the end of systolic contraction.[1] The volume of blood remaining in the ventricles during isometric relaxation is the ventricular residual volume which, together with the stroke volume, composes the diastolic ventricular volume or the volume of blood in the ventricular cavities during their isometric contraction. A knowledge of the diastolic ventricular volume is of physiological importance because diastolic stretch plays an important role in determining the dynamic and metabolic activity of the heart.[2,3,4] This diastolic stretch of the heart muscle cannot be estimated from the ventricular pressure curves since it has been shown that changes in ventricular filling and diastolic stretch can take place without increase in the distending pressure.[1] Therefore, an accurate concept of the diastolic stretch of heart muscle is only possible through knowledge of diastolic volume.

A knowledge of the residual volume is of further importance because utilization of part of this volume represents a mechanism by which the heart is able to increase its output.[5] Although the blood reservoir furnished by the residual volume is only available for some four to eight cardiac cycles, it is probably important in enabling the heart to cope with rapid demands for an increased circulatory blood volume. Hamilton and associates observed large changes in cardiac volume in response to bleeding and other experimental procedures in the dog. They concluded that the heart is an important part of the intrathoracic blood reservoir.[6]

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Aside from the physiological importance, an estimation of the residual volume is of clinical significance. It is known that in congestive failure circulation time is considerably prolonged. Nylin has demonstrated that a prolongation of the circulation time in this condition does not result from increased venous pressure and decreased cardiac output alone; it is also caused by the dilution of the test substance in the large residual blood volume of the heart.[7] Lysholm and co-workers showed also that the index, $\frac{\text{heart volume}}{\text{stroke volume}}$, is a reliable measure of heart function.[8] They showed that in healthy individuals of different sizes under standard conditions, the index, $\frac{\text{heart volume}}{\text{stroke volume}}$, is relatively constant. In patients with cardiac insufficiency, however, a considerable increase in this index ensued as a result of increased heart volume and reduced systolic discharge.

In the past, attempts to estimate the residual blood volume of the heart have relied mainly on measurements of the heart by roentgenogram in vivo or on the isolated heart in vitro by use of the water displacement method. The first attempt to determine the volume of the heart by x-ray examinations was made by Geigel.[9] The first practical method was worked out by Palmieri.[10] Most modern methods are based on roentgenological procedures of Rohrer[11] and Kahlstorff.[12] Using a constant which takes the shape of the heart into consideration, these investigators devised formulas for heart volume determinations. Their findings were confirmed by a series of authors.[13] According to these investigators, the heart volume of normal adults is approximately 700 c.c.[13] Nylin was able to show, by comparing pre- and post-mortem roentgenological determinations of the heart volume, that this volume decreased markedly after death.[14] This probably explains the large discrepancy found between in vivo and in vitro determinations. Recently the total volume of the dog's heart was determined with a formula devised by Hamilton and co-workers.[6]

Estimation of the capacity of the heart chambers in vitro usually involves filling the individual chambers with liquid wax and displacement of water by these wax casts.[15] Hochrein improved on these methods by dilating the heart with air pressure corresponding to 8 cm. of water and filling the heart chambers in this position with wax.[16] Hochrein concluded that the capacity of the right heart exceeded that of the left and that the atrial volumes exceeded those of the ventricles. He pointed out especially that the quantity of blood in the different chambers considerably exceeded the stroke volume.[16]

Studies on patients with heart failure were undertaken by Nylin[14] and by Friedman.[17] Both investigators came to the conclusion that the quantity of residual blood during life in severe myocardial failure may approach several liters. Friedman showed that over 50 per cent of the total volume of the heart during life consists of residual blood and that much larger volumes are present in patients with cardiac enlargement due to myocardial disease.[17]

The advent of cardiac catheterization[18,18a] and the use of Evans blue for hemodynamic studies[19,20] have suggested a different approach to the problem. This paper deals with an attempt to estimate the residual volume of blood in the

right ventricle by means of Evans blue dye (T 1824) injected directly into the right ventricle and suctioned from the pulmonary artery.* The technique, the calculations, and the assumptions involved will be described, and the results obtained in normal and diseased hearts will be discussed.

PROCEDURES

The catheter used is modified slightly from the conventional double lumen catheter.† The opening of the proximal twin catheter is occluded, and five smaller openings are drilled into this proximal twin catheter approximately 5 mm. apart. The openings vary in size, so that the largest one is closest to the pulmonary valve. This assures equal and rapid outflow of dye into the ventricle.

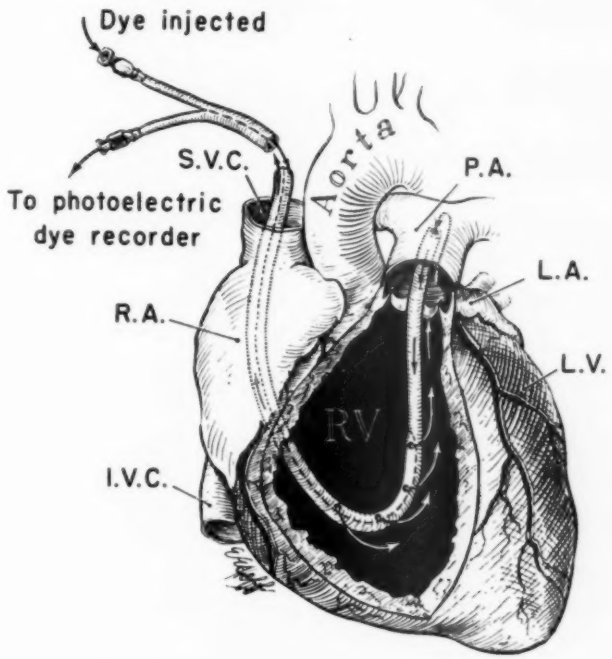

Fig. 1.—This shows the position of the double lumen catheter. The tip of the distal catheter lies in the main pulmonary artery. The end of the proximal catheter, with five openings, is situated in the in- and outflow tract of the right ventricle. Evans blue is injected through the ventricular catheter, and the blood-dye mixture is suctioned from the pulmonary artery through the photoelectric dye recorder.

The catheter is introduced until the opening of the distal twin catheter is situated in the main pulmonary artery and the five openings of the proximal twin catheter are in the in- and outflow portions of the right ventricle (Fig. 1). A sample of mixed venous blood is then collected through "the pulmonary catheter." Simultaneously, a sample of arterial blood is drawn from a peripheral artery, and the oxygen uptake is determined for the measurement of cardiac output with the

*Evans blue dye was obtained from William R. Warner & Co., Inc., New York, N. Y.
†Catheters were obtained from the U. S. Catheter and Instrument Company, Glens Falls, N. Y.

Fick principle. The "pulmonary catheter" is then connected to the cuvette of a photoelectric dye recorder by means of a sterile polyethylene tubing 70 cm. in length. The suction device, as well as the photoelectric dye recorder, has been described in a previous communication.[20] Small changes in the rate of suction through the cuvette cause relatively large alterations in slope. Therefore, great care should be taken to keep the rate of suction constant in all tests. The rate of flow through the cuvette was maintained at 12 c.c. per minute. This is the rate at which blood courses freely through the cuvette of the dye recorder. After the catheter is connected to the dye machine, suction is started through the "pulmonary catheter." Immediately afterward, 4 c.c. of Evans blue are injected from a calibrated syringe into the "ventricular catheter." During the injection and photographic recording of the dye curve, an electrocardiographic tracing is taken to record the heart rate. The changes in density of pulmonary artery blood

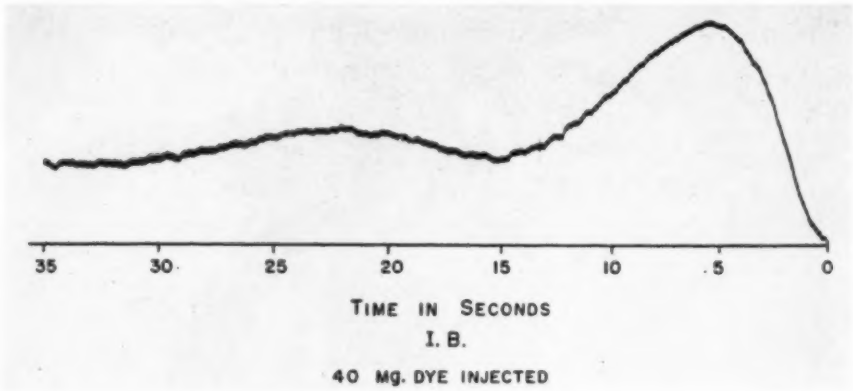

Fig. 2.—This illustrates an optically recorded dye curve from the pulmonary artery after injection of Evans blue into the right ventricle.

containing Evans blue are then recorded on photographic paper.[20] Fig. 2 illustrates such a tracing. This curve is then replotted on semilogarithmic paper according to the method of Hamilton and associates[21] (Fig. 3). The cardiac output may be determined from the dye dilution curve.[21] The downward slope of the dye dilution curve is calculated from the formula, slope $= \frac{1g\ C_1 - 1g\ C_2}{T_2 - T_1}$, where C_1 and C_2 represent two arbitrarily chosen dye concentrations on the dye dilution curve and T_1 and T_2 represent the time corresponding to these concentrations.

CALCULATIONS

Various methods for the calculation of the residual volume of the right ventricle from the dye dilution curve were attempted. By extrapolating the dye dilution curve to zero time, it was thought that the residual volume could be calculated from the equation:

$$1.\quad RV = \frac{Di}{C_0}$$

where RV equals residual volume, Di the amount of dye injected, and C_0 the concentration at zero

time. However, this was not possible because the downward slope of the curve is influenced by the length of the conducting system[20] and because the injection through the catheter is not instantaneous.

The possibility of calculating the residual volume from the following equation was also investigated:

$$2.\quad RV = \frac{SD}{\frac{C_1}{C_2} - 1}$$

where C_1 equals dye concentration before dilution with a succeeding systolic discharge. C_2 equals dye concentration after dilution with this systolic discharge. RV equals residual volume, and SD equals systolic discharge.

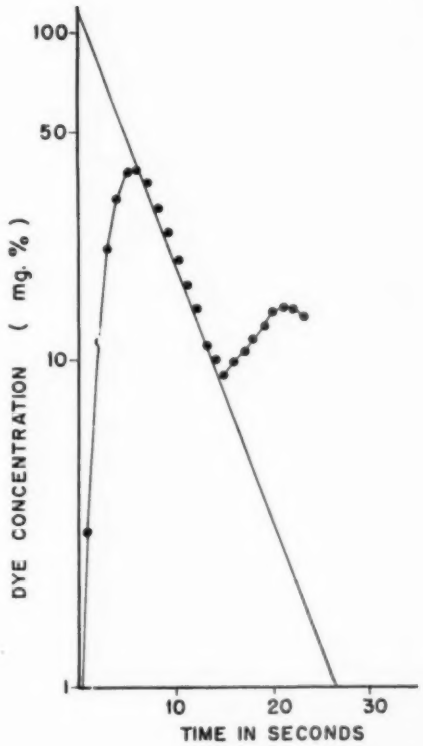

Fig. 3.—The dye curve from the pulmonary artery is plotted on semilogarithmic paper. The second peak is the result of recirculation.

This equation is derived as follows:

3. Amount of dye injected = $RV \times C_1$

After dilution of dye in right ventricle with one auricular systolic discharge:

4. Amount of dye injected = $(RV + SD) \times C_2$

Solving for 3 and 4:

5. $RV \times C_1 = (RV + SD) \times C_2$

6. $\frac{C_1}{C_2} = \frac{RV + SD}{RV}$

Dividing by RV:

7. $\frac{C_1}{C_2} = 1 + \frac{SD}{RV}$ or

$$8.\quad RV = \frac{SD}{\frac{C_1}{C_2} - 1}$$

Since the slope of the dye dilution curve is influenced by the conducting system,[20] the use of the formula is not possible in the system outlined above.

Analysis of the Factors Which Influence the Slope of the Dye Dilution Curve.—It has been shown by Hamilton and co-workers that the slope of the dye dilution curve varies with changes in the rate of flow.[19] Furthermore, Gernandt and Nylin have demonstrated that the appearance time of labeled red cells is dependent also on the heart volume.[22] The influence of the conducting system in altering the dye curve has been stressed in a preceding communication.[20] It is evident, therefore, that rate of flow, right ventricular blood volume, and the length of the conducting system must play a role in determining the dye dilution curve.

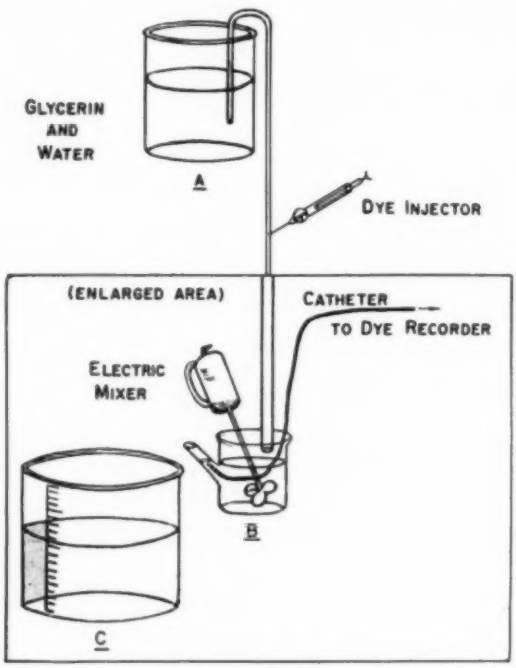

Fig. 4.—The artificial, nonpulsatile system devised to study the effect of flow, reservoir volume, and length of the conducting system on the downward slope of the dye dilution curve. *A* represents the chamber from which water or glycerol is siphoned through the reservoir chamber *B* into a graduated beaker *C*.

Several artificial systems were devised by means of which the influence of these factors could be studied. In the first system water was siphoned through a tubing into a fluid reservoir (Fig. 4). The volume in the fluid reservoir was kept constant by an overflow into a graduated cylinder. The rate of flow could thus be directly measured. The tip of a No. 8 catheter was placed directly into the overflow tube. This catheter was connected through polyethylene tubing with

the cuvette of the dye recorder. The dye was injected by means of a calibrated syringe into the tubing leading to the fluid reservoir. In order to get maximal mixing of the dye, an electrically operated stirrer was placed in the fluid reservoir. It should be noted particularly that the flow was not pulsatile.

The system permitted changes in the dilution of the dye by either altering the rate of flow or the capacity of the fluid reservoir. Since the length of the conducting system remained constant, the influence of changes in the rate of flow or the capacity of the reservoir on the slope of the dilution curve could be studied. By exclusion the influence of the conducting system could be examined.*

The results of a series of experiments with this nonpulsatile, artificial system are described in Fig. 5 in which the downward slope of the dye curve is plotted against the ratio of flow/reservoir volume. It should be noted that the reservoir volume in this relationship is RV actual of equation 16. Therefore, the ordinate in Fig. 5 may also be expressed as $\frac{\text{flow}}{\text{RV calc.}/C_F}$. Therefore, Fig. 5 represents the relationship of the slope of the dye dilution curve to the flow, the reservoir volume (RV actual), and the conducting system (C_F).

It may be seen that a linear relationship exists on semilogarithmic paper between the slope of the dye dilution curve and the ratio flow/reservoir volume.

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*Concentration at zero time which would have existed if the injection had been instantaneous is referred to as Co_A. This does not represent the true concentration of the dye at zero time, but differs from the actual concentration because of the influence of the conducting system. The actual concentration at zero time (Co_B), existing if the injection is instantaneous, can be directly obtained in the artificial system from the equation:

$$9.\quad Co_B = \frac{\text{mg. of dye injected}}{\text{volume of reservoir}}$$

The ratio of these two concentrations Co_A and Co_B must be the result of the influence of the conducting system or

$$10.\quad C_F = \frac{Co_B}{Co_A}$$

where C_F is the factor introduced by the conducting system (conducting factor). Using Co_A, a reservoir volume can be calculated.

$$11.\quad \text{RV calculated} = \frac{\text{mg. injected}}{Co_A}$$

The actual volume of the reservoir can be obtained from the formula:

$$12.\quad \text{RV actual} = \frac{\text{mg. injected}}{Co_B}$$

substituting equations 11 and 12 into 10.

$$13.\quad C_F = \frac{\text{mg. injected/RV actual}}{\text{mg. injected/RV calculated}}$$

$$14.\quad C_F = \frac{1/\text{RV actual}}{1/\text{RV calculated}}$$

$$15.\quad C_F = \frac{\text{RV calculated}}{\text{RV actual}}$$

$$16.\quad \text{RV actual} = \frac{\text{calculated RV}}{C_F}$$

The standard deviation is 0.14. Since the antilog of this figure equals 1.4, two-thirds of the observations of log $\frac{(\text{flow})}{(\text{RV})}$ should fall within ± 0.14 of the mean if the ratios of $\frac{\text{flow}}{\text{RV}}$ are plotted as their logarithms on a linear scale (Fig. 5). If the observed ratios, rather than their logarithms, are plotted on a logarithmic scale, two-thirds of the observations should fall between $\frac{(\text{regression mean})}{1.4}$ and (regression mean) $\times$ 1.4.

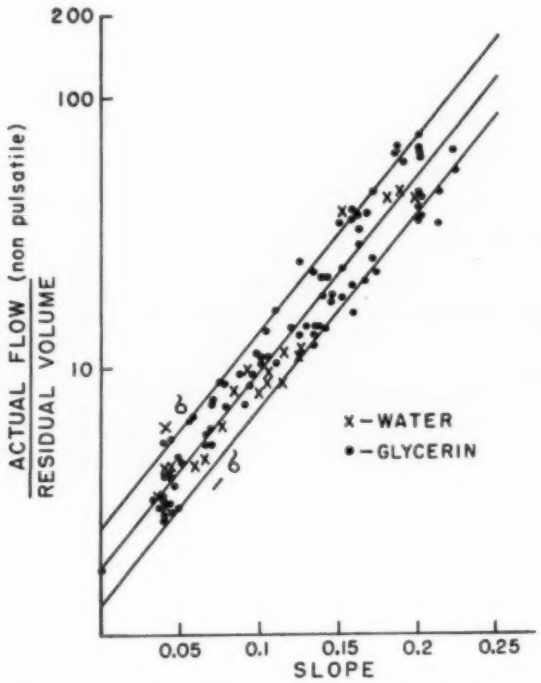

Fig. 5.—The relationship between the slope of the dye dilution curve and flow/reservoir volume as obtained from the artificial system illustrated in Fig. 4.

The system outlined did not permit the evaluation of the influence of the pulse rate on the relationship between the slope and the ratio of flow to residual volume. Furthermore, it failed to answer the question of whether the calculated volume represents the residual or the diastolic volume or a volume between these two.

An attempt was therefore made to answer these questions through the use of an artificial system in which the flow was pulsatile. Figs. 6 and 7 illustrate that in this system the pulse rate and residual volume, as well as the stroke and minute volumes, can be varied. Also, the minute flow, the stroke volume, and the residual volume can be directly measured and their influence on the dye dilution curve ascertained.

It may be seen that, similar to results obtained with the nonpulsatile experiments, the distribution of lg $\frac{(\text{flow})}{\text{RV}}$ is nearly symmetrical (Fig. 8). The standard deviation is 0.18. The antilog of 0.18 equals 1.5. This implies that about two-thirds of the observations of lg $\frac{(\text{flow})}{\text{RV}}$ should fall within $\pm$ 0.18 of the mean as given by the regression line if the ratios $\frac{\text{flow}}{\text{RV}}$ are plotted as their log-

Fig. 6.—Photograph of the artificial system, employing pulsatile flows. (National Institutes of Health, Photographic Research Section, FSA-PHS, No. 7680.)

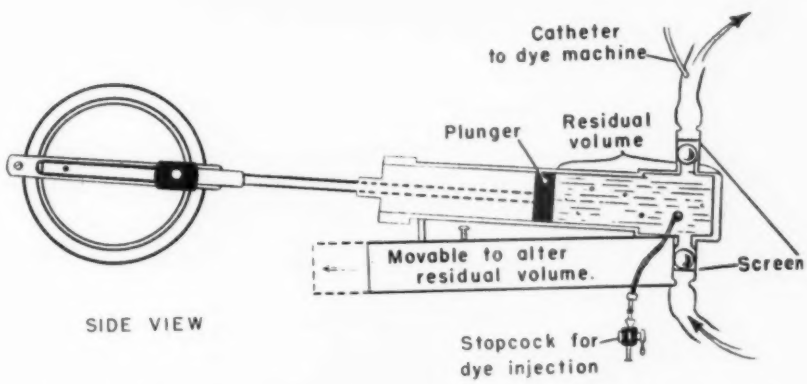

Fig. 7.—Diagram of the pulsatile artificial system. The "stroke volume" and "residual volume" can be altered and determined directly. Evans blue is injected directly into the pump. Water and dye mixture are suctioned from the tubing, representing the pulmonary artery, through the photoelectric dye recorder. The "pulmonary artery" is separated from the fluid chamber of the pump by a floating steel valve, representing the pulmonic valve. A similar valve separates the inflow tubing from the fluid chamber of the pump.

arithms on a linear scale (Fig. 8). Consequently, if the ratios $\frac{\text{flow}}{\text{RV}}$, rather than their logarithms, are plotted on a logarithmic scale, about two-thirds of the observations should fall between $\frac{(\text{regression mean})}{1.5}$ and (regression mean) $\times$ 1.5. Thus, at a slope of 0.2 the regression line indicates a value for the ratio $\frac{\text{flow}}{\text{RV}}$ of 50 (Fig. 8). About two-thirds of the observed ratios should lie in between the ratios $\frac{\text{flow}}{\text{RV}}$ (50/1.5 = 33 and 50 $\times$ 1.5 = 75). Therefore, for a given flow of

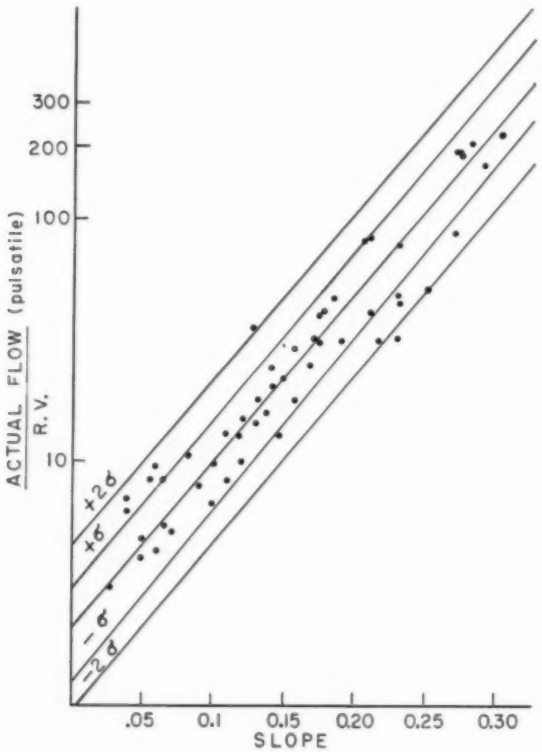

Fig. 8.—Data from the pulsatile system, relating the slope of the dye dilution curve to the ratio $\frac{\text{flow}}{\text{residual volume}}$.

5,000 c.c. per minute and a slope of 0.2, the upper and lower limits for residual volume for two-thirds of the observations will be 150 and 67 c.c., respectively. Since the standard deviation of lg $\frac{(\text{flow})}{\text{RV}}$ is constant, the same factor of 1.5 will apply in obtaining upper and lower limits for two-thirds of the observations.

A comparison with Fig. 5, which illustrates the data obtained with the nonpulsatile system, reveals that, although the regression lines are identical, the

scatter of data is slightly greater in the pulsatile system. It is possible that this is the result of variations in stroke volume and of inadequate mixing of the dye with water and glycerin.

It is now possible to calculate the residual volume from the relationship between slope and flow/RV as obtained in the pulsatile system (Fig. 8). Theoretically, either the flow as calculated by the Fick principle or the flow obtained from the dye curve may be used in this computation. However, in the calculations reported in this paper, only the cardiac output as determined by the Fick principle was used.

TABLE I. RESIDUAL VOLUME DETERMINATIONS IN FOURTEEN HOSPITAL PATIENTS WITHOUT CARDIAC ABNORMALITIES

NAME	DATE	SURFACE AREA	CARDIAC OUTPUT (FICK) (C.C. PER MINUTE)	RESIDUAL VOLUME (C.C.)	RESIDUAL VOLUME (C.C. PER M.^{2})	HEART RATE (PER MINUTE)	STROKE VOLUME (C.C.)	$\frac{RV}{SV}$
R.S.	7/19/50	1.76	7100	141	80	80	89	1.59
H.I.	7/27/50	1.54	4300	32	21	70	62	0.51
J.D.	9/ 9/50	1.90	4650	59	31	120	38	1.55
M.H.	9 20 50	1.62	5380	35	21	100	54	0.65
G.A.	10 18/50	1.52	3920	60	39	97	40	1.50
W.B.	10 23/50	1.92	4950	45	24	80	62	0.72
B.D.	11/ 3/50	1.82	3800	158	87	90	42	3.71
B.L.	11/ 6/50	1.48	3650	33	22	80	41	0.81
H.D.	11/ 7/50	1.69	6430	104	62	120	53	1.96
J.A.	10 12/50	1.72	3400	130	76	120	28	4.67
M.C.	11 21/50	1.65	7200	160	97	120	60	2.68
M.F.	11/14/50	1.64	4850	23	14	115	42	0.55
B.K.	11 24/50	2.00	8900	142	71	120	74	1.93
P.A.	7/14/50	1.95	5150	124	64	75	69	1.80
Average			5250	89	50		54	1.75

RESULTS

The results obtained in normal individuals are illustrated in Table I and Figs. 9 and 10. It may be seen from Table I that the cardiac output in these patients ranged from 3,400 to 8,900 c.c. per minute, with an average of 5,250 c.c. per minute. The residual volume varied from 23 c.c. to 160 c.c., with an average of 89 c.c. The scatter was slightly reduced when the residual volumes were calculated per square meter of body surface (Table I, Fig. 10). Lysholm and coworkers also found good correlation between heart volume and body surface.[8] The values for RV per square meter ranged from 14 c.c. to 97 c.c., with an average of 50 c.c. Nylin and Friedman reported a residual volume of the normal heart of approximately 400 c.c.[17,22] If the residual volume in all four cardiac chambers is identical, the right ventricle should contain approximately 100 c.c. Therefore, the figure obtained on normal individuals with the procedure described in this paper agreed well with values obtained by Nylin and associates.

Values for the ratio $\frac{\text{residual volume}}{\text{stroke volume}}$ are summarized in Table I. It may be seen that the average ratio in the normal individuals of this series was 1.75. This indicates that the amount of blood remaining in the right ventricle after the systolic ejection usually exceeded the stroke volume.

The results obtained in four patients with myocardial failure are illustrated in Table II and Figs. 9 and 10. All patients had an increase in the transverse

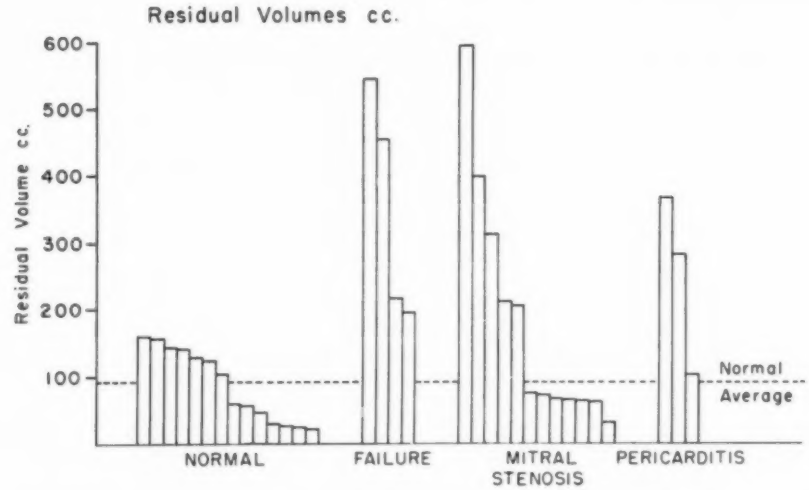

Fig. 9.—Data obtained on the residual volume of the right ventricle. There are considerable variations in the residual volumes of normal individuals and patients with mitral stenosis. The right ventricular residual volumes are increased in two patients with adhesive pericarditis. In one patient with constrictive pericarditis, the residual volume is normal.

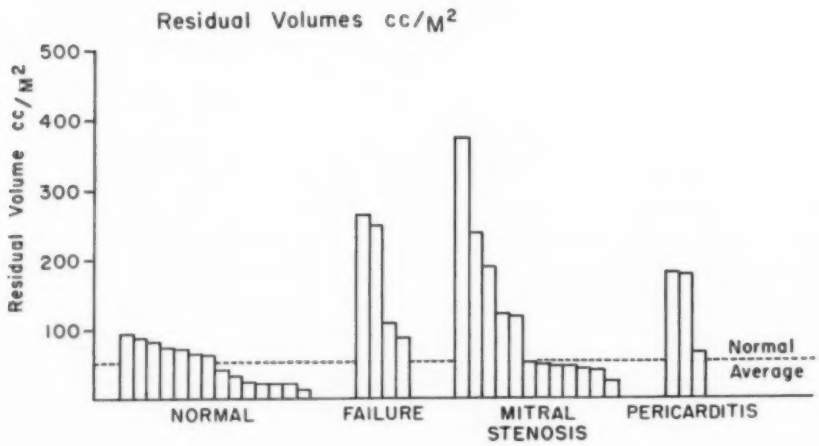

Fig. 10.—This illustrates right ventricular residual volumes per square meter of body surface. The scatter of data is considerably less than in Fig. 9.

diameter of the heart and increased hilar markings in the lung fields. One (W. L.) had a left hydrothorax. With the exception of one (A. R.), all had dyspnea and orthopnea. Peripheral edema was present in all but one patient (A. R.). One patient (W. L.) had swelling of the abdomen. Table II illustrates that the cardiac output and the stroke volume of these patients were reduced. The observed residual volumes varied from 192 to 542 c.c., with an average of 350 c.c. The residual volume per square meter of body surface averaged 176 c.c. as compared to 50 for normal individuals. It is evident from these observations that the ratio of $\frac{\text{residual volume}}{\text{stroke volume}}$ must be elevated. Table II shows that the average ratio was 13.6 as compared to a normal ratio of 1.75. Lysholm was of the opinion that an index of $\frac{\text{heart volume}}{\text{stroke volume}}$ above 13.5 during rest indicates an infringement on cardiac reserve.[8]

TABLE II. RESIDUAL VOLUME DETERMINATIONS IN FOUR PATIENTS WITH HYPERTENSIVE CARDIOVASCULAR DISEASE AND ARTERIOSCLEROTIC HEART DISEASE WITH FAILURE

NAME	DATE	DIAGNOSIS*	SURFACE AREA	CARDIAC OUTPUT (FICK) (C.C. PER MINUTE)	RESIDUAL VOLUME (C.C.)	RESIDUAL VOLUME (C.C. PER M.²)	HEART RATE (PER MINUTE)	STROKE VOLUME (C.C.)	$\frac{RV}{SV}$
A.R.	10/20/50	HCVDcF	2.0	1730	192	86	100	17	11.30
N.F.	1/29/51	HCVDsF	2.0	4670	213	105	75	62	3.44
W.L.	10/ 2/50	ASHDcF	2.2	2320	542	245	100	23	23.5
M.W.	11/20/50	ASHDcF	1.7	2630	455	264	95	28	16.2
Average				2837	350	176		35	13.6

*HCVD = hypertensive cardiovascular disease
F = failure
ASHD = arteriosclerotic heart disease

The findings in twelve patients with mitral stenosis are illustrated in Table III and Figs. 9 and 10. The residual volumes varied from 21 to 372 c.c. per square meter. The scatter of data in this group was, therefore, considerably greater than in normal individuals, although all values were expressed per square meter of body surface. This is probably the result of the presence or absence of right ventricular failure in patients with mitral disease. In most of the patients in whom the residual volumes were normal, clinical signs of congestive failure were absent, and radiological examination revealed only enlargement of the left auricle and of the pulmonary arteries (M. U., K. M., and J. E.). However, agreement as to the degree of right ventricular failure as determined from clinical findings and from determinations of the residual volume is not always good. For example, one patient (R. O., Table III) had a residual volume of 372 c.c. per square meter. On fluoroscopy the left auricle was considerably enlarged, but the right ventricle showed only slight enlargement. The reason for this difference is not clear.

TABLE III. RESIDUAL VOLUME DETERMINATIONS IN TWELVE PATIENTS WITH MITRAL DISEASE

NAME	DATE	SURFACE AREA	CARDIAC OUTPUT (FICK) (C.C. PER MINUTE)	RESIDUAL VOLUME (C.C.)	RESIDUAL VOLUME (C.C. PER M.^{2})	HEART RATE (PER MINUTE)	STROKE VOLUME (C.C.)	$\frac{RV}{SV}$
M.U.	10/19/50	1.45	3600	66	46	110	33	2.00
B.E.	10/10/50	1.72	5250	202	118	73	72	2.81
R.O.(AF)	10/ 6/50	1.59	4380	591	372	140	31	19.10
G.R.	10/ 5/50	1.66	3020	303	185	100	30	10.24
K.M.	11/ 1/50	1.44	3430	64	44	120	28	2.28
B.I.	9/18/50	1.46	4670	73	50	90	52	1.40
R.E.(AF)	11/13/50	1.55	3340	62	40	80	42	1.47
K.I.	2/51	1.70	6330	395	234	80	79	5.02
L.W.	1/23/51	1.64	7760	71	44	100	78	1.03
J.E.	12/12/50	1.70	5070	67	39	80	63	1.05
B.G.	1/ 3/51	1.85	3330	207	113	86	39	5.34
S.C.	1/24/51	1.50	2300	31	21	100	23	1.35
Average			4460	178	110		47.5	4.45

The findings in three patients with constrictive and adhesive pericarditis are illustrated in Table IV and Figs. 9 and 10. In one patient (B. W.) the residual volume was within normal limits, but the ratio $\frac{RV}{SV}$ was elevated. This patient represented clinically the typical picture of constrictive pericarditis.[24] There was ascites with distention of the neck veins, and the liver was enlarged. Physiologically, this patient showed slight elevation of the pulmonary arterial pressure, and the right auricular and ventricular pressure tracings were characteristic of constrictive pericarditis.[24a] On fluoroscopy, there was some fullness of the right ventricular border, but, in general, the heart was not greatly enlarged. On the other hand, the two remaining patients in this group showed large residual volumes and a significant increase in the ratio $\frac{\text{residual volume}}{\text{stroke volume}}$ (Table IV, Figs. 9 and 10). Both patients had signs of venous congestion with elevated venous pressure and a large liver. On fluoroscopy, the hearts of these patients were found to be enlarged, and the pulsation over the left ventricular curvature was diminished. It seemed of importance that in one of these patients (W. N.) the heart failed to shift in the chest when the position of the patient was changed. Both patients had decreased cardiac output. W. N. had elevation of the pulmonary arterial pressure. The enlargement of the heart, together with evidence of diminished cardiac border movements and the fixation of the heart in the thorax on changing the position, indicates the presence of myocardial disease with external adhesive pericarditis rather than of classical constrictive pericarditis.

DISCUSSION

The method described in this report deals with an attempt to calculate the residual volume of blood in the right ventricle from a falling concentration of

Evans blue in the pulmonary artery after injection of the dye into the right ventricle. The chief difficulty lies in the fact that the slope of the dye dilution curve is determined not only by the rate of flow of blood from the ventricle into the pulmonary artery[19] and by the dilution of dye by ventricular blood, but also by the length of the tubing connecting the pulmonary artery with the cuvette of the photoelectric dye recorder.[20] It is for this reason that calculations involving the uncorrected slope of the dye dilution curve or the relationship between stroke volume and successive dye concentrations in the pulmonary artery are not feasible. The possibility remains, however, to approach the problem on an empirical basis. Therefore, two artificial systems were devised in which the length of the conducting system remained constant, and all volumes and flows could be determined by direct observation. In the first of these systems the flow is nonpulsatile (Fig. 4). The results obtained with this system show a linear relationship on semilogarithmic paper between the slope of the dye dilution curve and the ratio of flow/reservoir volume (Fig. 5). As all data in Fig. 5 are obtained from direct measurements only, the influence of the conducting system on the slope of the dye dilution curve is contained in the relationship of slope against $\frac{\text{flow}}{\text{RV}}$, and no further corrections for this factor are necessary. If the observed ratios of $\frac{\text{flow}}{\text{RV}}$ are plotted on a logarithmic scale, two-thirds of the observations fall between $\frac{(\text{regression mean})}{1.4}$ and (regression mean) $\times$ 1.4. This relatively large scatter cannot be attributed to changes in volume because, due to the absence of pulsatile flows, the volume of the reservoir remains constant. Recirculation also cannot be responsible, because the water or glycerin dye mixture does not recirculate through the cuvette of the photoelectric dye recorder. It is possible that the deviations from the regression line may result partially from errors in ascertaining correctly the slope of the dye dilution curve. However, the principal causes of the scatter remain obscure.

TABLE IV. RESIDUAL VOLUME DETERMINATIONS IN THREE PATIENTS WITH ADHESIVE AND CONSTRICTIVE PERICARDITIS

NAME	DATE	SURFACE AREA	CARDIAC OUTPUT (FICK) (C.C. PER MINUTE)	RESIDUAL VOLUME (C.C.)	RESIDUAL VOLUME (C.C. PER M.^{2})	HEART RATE (PER MINUTE)	STROKE VOLUME (C.C.)	$\frac{\text{RV}}{\text{SV}}$
W.N.	12/4/50	1.57	1960	280	178	80	25	11.2
W.E.	1/2/51	2.04	4370	365	179	87	50	7.31
B.W.	9/7/50	1.63	3360	99	61	100	34	2.91

The nonpulsatile system does not permit the evaluation of the influence of the pulse rate on the relationship between slope and the ratio of flow/residual volume. Furthermore, the residual volume of the right ventricle in vivo, as cal-

culated from the regression line in Fig. 5, could represent the residual or diastolic volume or a volume between these two. The artificial system described in Figs. 6 and 7 attempts to answer these questions. Similar to the nonpulsatile system described, the "minute volume" and the "residual volume" can be measured directly. In addition, the "stroke volume" can be determined, and alterations in the "stroke and minute volumes" are possible through changes either in the "pulse rate" or the position of the piston (Figs. 6 and 7). In order to imitate as closely as possible the conditions existing in vivo, the catheter is inserted into a rubber tubing representing the "pulmonary artery" (Fig. 6) which is separated from the "ventricle" by a ball valve. Since, as in the nonpulsatile system, volume and flows are directly observed, the influence of the conducting system on the slope of the dye curve is again contained in the relationship of slope to $\frac{\text{flow}}{\text{RV}}$, and no further correction for this factor is necessary. The data obtained with the pulsatile model show a slightly greater degree of scatter than those obtained from the nonpulsatile system (Fig. 8). The standard deviation is lg 0.18, which implies that two-thirds of the observations, plotted on a logarithmic scale, fall between $\frac{\text{(regression line)}}{1.5}$ and (regression line) $\times$ 1.5.

Some of the possible reasons for this scatter have already been dealt with. It is possible that in the pulsatile system variations in the rate of injection and stroke volume, as well as inadequate mixing, also play a part. Under ideal conditions the injection should be made during the isometric relaxation phase of the right ventricle only. This is obviously not possible. Since the infusion lasts for a period of approximately five seconds, the slope of the dye dilution curve will ordinarily correspond to a ventricular volume which probably is between the residual and diastolic volume. However, the relationship $\frac{\text{flow}}{\text{RV}}$ represented by the ordinate in Fig. 8 is obtained from directly observed values for flow and for residual volumes. It is possible, therefore, that the slopes represented are not strictly related to the observed ratios of $\frac{\text{flow}}{\text{RV}}$. However, it is unlikely that this factor is of great importance, since almost equal deviations from the regression line are found in the nonpulsatile system.

It is not possible to state the accurate relationship between the slope of the dye dilution curve and the ratio $\frac{\text{flow}}{\text{RV}}$ for the human right ventricle. The data obtained with the artificial models indicate, however, that the results obtained on the human heart in vivo are only approximations.

The data on the right ventricle of normal hearts show large variations; the residual volumes vary from 23 to 160 c.c. (Table I, Figs. 9 and 10). Fig. 10 and Table I illustrate that the scatter is slightly reduced when residual volumes are expressed per square meter of body surface. A similar correlation between surface area and total heart volume was found by Lysholm and co-workers.[8] The average residual volume of the right ventricle is 50 c.c. per square meter. The

figure agrees with the value obtained by Nylin and by Friedman.[14,17] The ratio $\frac{\text{residual volume}}{\text{stroke volume}}$ in the normal right ventricle averages 1.7. This indicates that the systolic discharge is less than the residual volume.

In the four patients with clinical evidence of myocardial failure and enlargement of the right ventricle, the cardiac output and stroke volumes were reduced. All showed significant increase in the residual volume of the right ventricle (Table II, Figs. 9 and 10). Consequently, the ratio of $\frac{\text{residual volume}}{\text{stroke volume}}$ was elevated in these patients. Large ratios of $\frac{\text{heart volume}}{\text{stroke volume}}$ in patients in failure are also described by Lysholm and co-workers.[8] This confirms the findings of Huckabee and co-workers that "it appears justifiable to define heart failure as a condition in which the cardiac output is inadequate in relation to the filling load."[21]

The important role which large residual and diastolic volumes must play in the dynamic and metabolic response of the failing myocardium is difficult to deny. Starling recognized this factor when he formulated the now well-known relationship between the diastolic volume of the heart and the initial fiber tension existing at the onset of systole.[2a]

Starling and Visscher believed that the relation between diastolic ventricular volume and oxygen usage is, within limits, a linear one.[2] The validity of this relationship in the failing human heart has recently been questioned.[3] In patients with failure described in this report, this failure resulted from hypertension and arteriosclerosis. For that reason, left ventricular diastolic volumes were probably also increased. It has been shown, however, that in cardiac failure the resting oxygen consumption per unit of left ventricular muscle is normal, although the diastolic volume in these patients is increased.[3] It is possible that, in contrast to acute changes in load, a slowly progressing increase in initial fiber tension does not result in significant changes in the oxidative myocardial metabolism.

Considerable variations in residual volume were present in patients with mitral stenosis, even if the data were expressed per square meter of body surface (Table III, Figs. 9 and 10). Correlation with the clinical and radiological data indicates that the residual volumes were enlarged in patients with right ventricular failure. However, in one patient in whom the residual volume was 372 c.c. per square meter, the right ventricle showed only slight enlargement. The reason for this discrepancy is not understood.

It has been shown that some of the physiopathological manifestations of mitral disease are indistinguishable from myocardial failure.[25] Decreased cardiac output, increased arteriovenous oxygen difference, and elevated pulmonary artery and capillary pressures at rest can occur in mitral disease as well as in myocardial failure. A rise in pulmonary artery pressure from rest to exercise is equally frequent in myocardial and in mitral disease. Recognition of myocardial failure in the presence of mitral disease is of some importance because of the additional surgical risk involved in operation on the mitral valve in the presence of myo-

cardial failure. It is possible that the measurement of the residual volume may furnish a tool in estimating the degree of right ventricular failure accompanying mitral disease.

In one patient with the characteristic clinical and physiological signs of constrictive pericarditis, the residual volume was normal although the ratio $\frac{\text{residual volume}}{\text{stroke volume}}$ was elevated (Table IV, Figs. 9 and 10). High values of $\frac{\text{residual volume}}{\text{stroke volume}}$ are also present in patients with congestive failure. This, however, results from decreased stroke volume and increased residual volume. In the patient with constrictive pericarditis, however, the increase in this ratio resulted only from a decrease in stroke volume. This finding is in line with the concept that the basic physiological abnormality in constrictive pericarditis consists in an impediment in diastolic filling and/or systolic emptying of the ventricle. This results in decreased stroke volume with little change in residual volume.[26]

The two remaining patients in the group summarized in Table IV had enlarged hearts on fluoroscopy with diminished pulsations over the left ventricular curvature. Signs of venous congestion were also present. The right ventricular residual volumes were significantly elevated (Table IV) (178 and 179 c.c. per square meter of body surface). The ratio of $\frac{\text{residual volume}}{\text{systolic discharge}}$ was elevated to 11.2 and 7.3, respectively. In these two patients, as in the patients with myocardial failure, the increase in the ratio $\frac{RV}{SV}$ is the result of decreased stroke volume and of increased residual volume. This indicates that, in addition to mechanical impairment to filling or emptying of the ventricle, myocardial failure may have been present.

SUMMARY

A method has been described which attempts the estimation of the residual and diastolic blood volumes of the right ventricle of normal and diseased human hearts. The procedure consisted of catheterization of the right ventricle and the pulmonary artery with a double lumen catheter and the injection of Evans blue into the right ventricle. The residual volumes were then estimated from the slope of the photographically recorded dye dilution curve.

Two artificial circulation models were used to test the accuracy of the method and to establish the relationship between the various factors which influence the downward slope of the dye dilution curve. The theoretical implications and the accuracy of the method were discussed.

Data on the residual volume of normal right ventricles showed large scatter which was reduced when the volumes were expressed per square meter of body surface. The average right ventricular residual volume was found to be 50 c.c. per square meter. The ratio $\frac{\text{residual volume}}{\text{stroke volume}}$ in the normal right ventricle was 1.7.

Large residual volumes were found in patients with right ventricular failure, and the ratio $\frac{\text{residual volume}}{\text{stroke volume}}$ was significantly elevated (average 350 c.c. and 13.6, respectively).

Considerable variations in the right ventricular residual volume were present in patients with mitral stenosis, even if the data were expressed per square meter of body surface. Correlation with clinical data revealed that, in patients with mitral stenosis and large residual volumes, right heart failure was usually present.

In one patient with constrictive pericarditis, the residual volume was normal, but the ratio $\frac{\text{stroke volume}}{\text{residual volume}}$ was increased. Larger residual volumes were found in two patients suffering from adhesive pericarditis.

The physiological implications of the results obtained were discussed.

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STUDIES ON THE MECHANISM OF VENTRICULAR ACTIVITY

I. THE NATURE OF THE P-R INTERVAL

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IN BOTH man and experimental animal, the fact has been established that only a fraction of the normal P-R interval represents passage of the excitation impulse across the auricular myocardium. Lewis[1] calculated that the speed of the impulse in the dog's auricle during normal sinus rhythm is approximately 1,000 mm. per second. By means of simultaneous esophageal leads, the normal impulse in the human auricle has been found to travel at a rate of at least 500 mm. per second.[2] If these determinations are accurate, the cardiac impulse traverses the auricles from the sinoauricular node to the A-V node in approximately 0.05 second, or in about one-third of the period occupied by the P-R interval in the normal electrocardiogram. The purpose of this communication is to present new data concerning the delay in conduction responsible for the remaining portion of the normal P-R interval.

CURRENT THEORIES

Two theories have been advanced to account for the final portion of the P-R interval in the normal electrocardiogram. The most widely accepted theory, supported by Sir Thomas Lewis, assumes a slowing of conduction in the A-V node. The alternative explanation, known as the "latency theory," postulates that the excitation impulse pauses for a prolonged period at the periphery of the A-V conduction system before activating the ventricles. The differences between these two concepts are illustrated in Fig. 1.

Evidence for the latency theory is found in the writings of Erlanger,[3,4] Straub,[5] and Mobitz.[6] According to the original concept proposed by Erlanger in 1905, the cardiac impulse travels rapidly from the sinus node through the auricles and A-V conducting tissue to the periphery of the conduction system; upon reaching the junction between specialized tissue and ventricular muscle, it undergoes a latent period before evoking a ventricular response. A variation of the latency theory was suggested by Mobitz, who distinguished an auricular and a ventricular portion in the A-V node of the calf's heart and proposed that the normal delay in conduction consists of stoppage of the impulse in the ventricular part of the node. Prior to Erlanger, physiologists assumed that a delay in conduction occurred in the bundle of His. This belief was founded on the slenderness of the structure through which the impulse must pass on its way from the auricles to the ventricles. The assumption seemed justified by the studies of Gaskell[7] on the delay suffered by an impulse

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in passing over artificially made bridges. However, this theory was abandoned when Erlanger pointed out that the slow conduction through bridges or compressed areas is the result of injury. In studies of a direct nature on this problem, Erlanger observed that the sum of the reaction time of the ventricles to direct stimulation and the time required for the transmission of the impulse from the auricles to the ventricles was very close to the As-Vs interval in most of his experiments. From these observations, he noted that "the As-Vs interval is accounted for by a relatively small part of the time consumed by the impulse in traveling with considerable velocity through the tissue

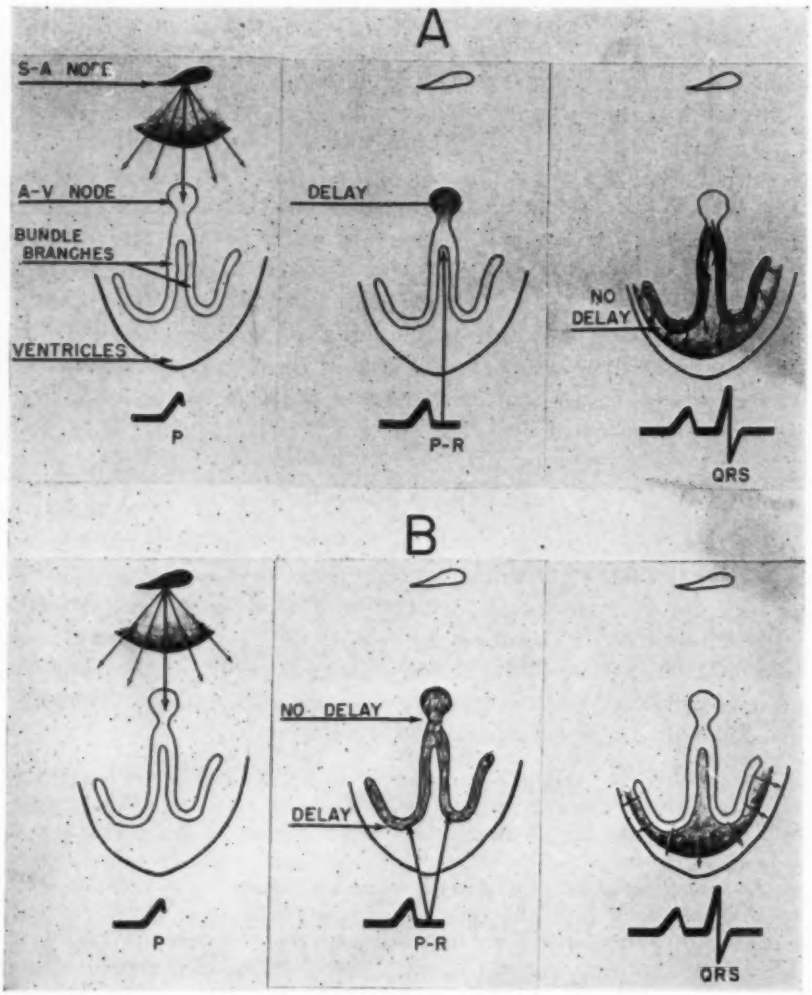

Fig. 1.—Diagrammatic illustration of two alternative theories concerning the delay in A-V conduction responsible for the major portion of the P-R interval in the normal electrocardiogram.

A, The normal impulse passes from the sinus node to the A-V node as the initial part of the P wave is inscribed. The remainder of the P-R interval is recorded while the impulse is transmitted slowly through the A-V node. After the delay in the node, the impulse rapidly passes over the remaining portions of the conduction system and activates the ventricles during inscription of the QRS.

B, No delay in conduction occurs until the impulse reaches the periphery of the A-V conduction system. The major portion of the P-R interval is written while the impulse pauses at the peripheral barrier; then conduction is resumed, and the QRS is inscribed as ventricular depolarization occurs.

of the conducting system. The remainder of the interval may be attributable to a latency occurring at some point of transition of one type of tissue to another."

An excellent criticism of the latency theory was presented by Ashman[8] in 1930. This author pointed out that the partial heart block which follows an interpolated auricular extrasystole can best be explained on the basis of slow conduction through the A-V conduction system. Furthermore, the observation that a normal ventricular complex may follow an interpolated ventricular extrasystole is inconsistent with Erlanger's assumption of latency at the periphery of the conduction system. Finally, experimental study indicates that an electrical impulse in the A-V node dies out unless it is transmitted within 0.3 second; hence, the occurrence of P-R intervals as long as 1.0 second cannot be explained by the latency theory, since an impulse undergoing a prolonged pause in the conducting tissue would be unable to resume its journey and would fail to activate the ventricles.

The theory of slow conduction in the A-V node is principally the result of electrocardiographic studies reported by Lewis in 1925.[1] By demonstrating the presence of an unexplained interval between the onset of electrical negativity at the A-V node and the first demonstrable ventricular negativity, Lewis established that a delay in conduction occurs somewhere between the caudal region of the auricle and the ventricular muscle. On the basis of indirect evidence, this delay was attributed to slow transmission in the A-V node. In contrast to the latency theory which assumes stoppage of the cardiac impulse at a single site, Lewis considered the impulse to progress at all times during its journey through the A-V conduction system but at a varying speed. The rate of transmission in the A-V node was deduced from Lewis' law of cardiac muscle.

Hering[9] had attempted to localize the delay by direct experimental methods. He claimed that it was possible, in the dog, to so stimulate both electrically and mechanically the cut surfaces of the auriculoventricular bundle that the stimulus did not escape to the surrounding structures. Erlanger believed that Hering's conclusion should be accepted with caution, and Lewis states: "His observations cannot, I think, be accepted unreservedly."[1] Recently, Turman and Robb[10] attempted to record depolarization of the A-V bundle but were unable to conclude with certainty that this result had been accomplished.

Although the concept of slow transmission through the A-V node has achieved wide acceptance, no conclusive evidence of the precise site of the normal delay in A-V conduction has yet been obtained. As Wiggers[11] noted, "Owing to the inaccessibility of the node and the difficulty of establishing the precise moments of electrical negativity in different regions of the junctional tissue, our evidence for such a retardation (in the A-V node) is necessarily indirect." He concludes, "It is not surprising that the existence of the delay being at the A-V node should have been questioned."

AUTHORS' STUDY

After examining the experimental evidence summarized, we also were convinced that the site of the normal delay in A-V conduction had not been satisfactorily demonstrated. Our interest in this problem arises from an experimental study of the Wolff-Parkinson-White syndrome[2,12] during which a variety of shortened P-R intervals and widened QRS complexes were produced in at least fifty animals by subthreshold stimulation of numerous sites on the epicardium or endocardium of the ventricles or on the A-V node. Two observations established that A-V conduction during the experimentally produced syndrome took place through the normal conducting system: (1) The same procedure which produced Wolff-Parkinson-White complexes when applied to the intact heart failed to evoke such complexes after the bundle of His was cut, and (2) electrocardiographic patterns simulating all varieties of the clinical syndrome were ob-

tained by stimulation of various ventricular sites far removed from any known aberrant (anatomic) A-V pathway. From these observations the conclusion was drawn that our experimental procedure had overcome the delay which normally occurs in the A-V conduction system, resulting in premature arrival of the impulse at a ventricular focus with consequent shortening of the P-R interval and widening of the QRS. If, therefore, the normal delay in A-V conduction consists of latency at the periphery of the conducting tissue, the Wolff-Parkinson-White pattern obtained in our experiments must represent premature transmission of the impulse through the peripheral barrier. If, on the other hand, the normal delay is due to slow conduction through the A-V node, the Wolff-Parkinson-White pattern represents accelerated transmission through the node. It thus became apparent that the mechanism of the Wolff-Parkinson-White syndrome could not be fully elucidated until the exact site of the normal delay in A-V conduction was determined.

Methods.—Direct evidence of the site of the normal delay in A-V conduction was obtained by the following method: Ectopic foci were established by electrical stimulation at successively lower levels of the A-V conduction system in the dog's heart while electrocardiograms were recorded at double speed (50 mm. per second) on a Sanborn Poly-Viso electrocardiograph. The interval between the appearance of the stimulus at the ectopic focus and the onset of the ventricular response was determined by careful measurement of the Stim-QRS interval in the electrocardiograms. A comparison of the Stim-QRS intervals in tracings from a given animal recorded while stimuli were applied at different levels of the conduction system revealed whether or not a delay in conduction had occurred between the sites of stimulation. If the Stim-QRS interval was longer when a higher level of the conduction system was stimulated than when a lower level was stimulated, a delay in conduction was demonstrated to occur somewhere between the two foci. If the Stim-QRS intervals were identical in tracings recorded while stimuli were applied at different sites on the conducting tissue, the fact was established that no delay in conduction occurred between the sites stimulated.

Experiment 1.—A small stimulating electrode, insulated except for a tip approximately the size of a pinhead, was introduced into the right auricle through a purse-string opening. The tip of the electrode was placed low in the auricle in the region of the A-V node, and an alternating current was generated from a pulsating stimulator connected to the electrode. Stimuli were administered through this system at a rate faster than the normal sinus rate, enabling the experimentally produced focus to become the cardiac pacemaker. The same electrode was then passed through the tricuspid valve to a position directly over the bundle of His, and stimuli again were sent through the electrode at a rate faster than normal sinus rhythm. Double speed electrocardiograms were recorded throughout the experiment.

Much practice, patience, and precision were required to locate the stimulating electrode on the ventricular septum at a site directly over the bundle of His. The position of the electrode was verified by the shape of the QRS complex: If the electrode was over the bundle of His, stimuli were conducted along the normal A-V pathway, and the resulting QRS was normal in width and direction

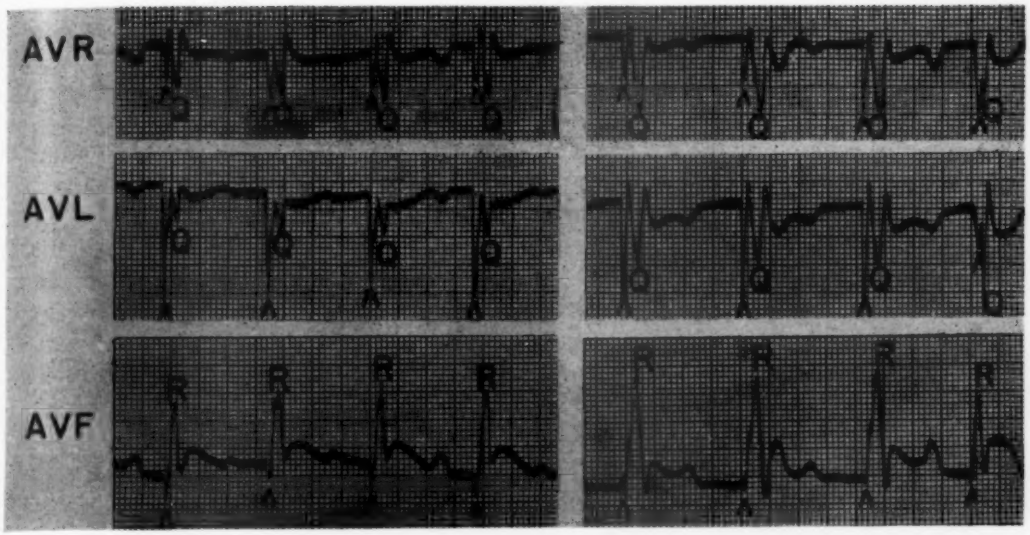

Fig. 2.—Simultaneous leads recorded at double speed (50 mm. per second). *A*, Normal QRS complexes inscribed when the stimulating electrode was on the bundle of His. *B*, Abnormally wide and distorted QRS complexes inscribed when the stimulating electrode was moved a few millimeters from the bundle of His.

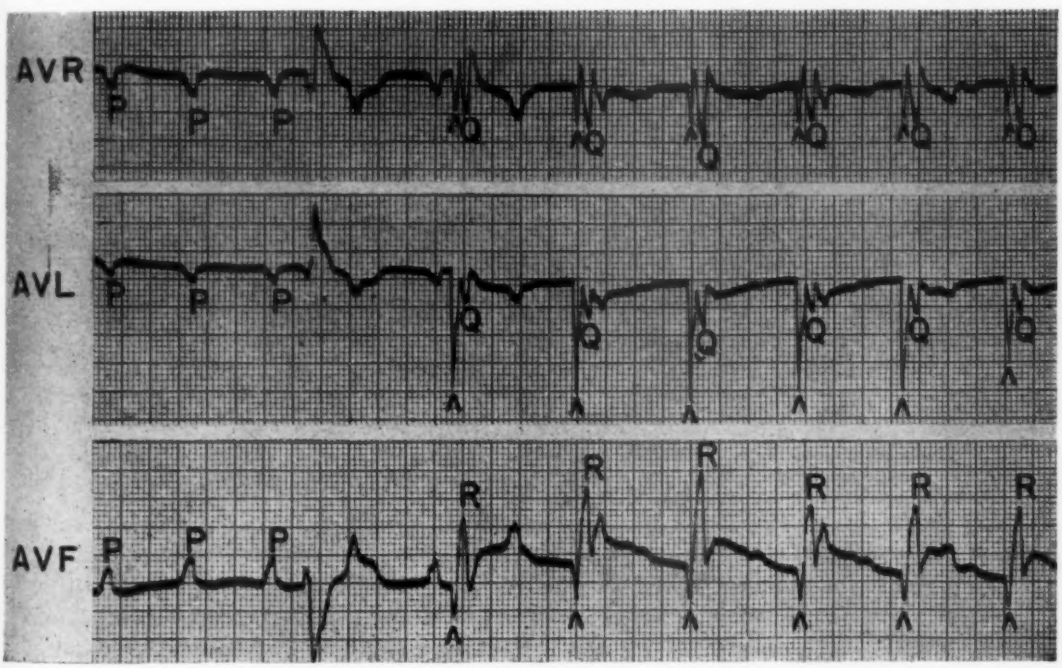

Fig. 3.—Simultaneous leads recorded at double speed (50 mm. per second) showing complete heart block produced by pressure applied to the electrode on the bundle of His. When stimuli are administered through the electrode on the bundle, normal QRS complexes are obtained.

in each of three simultaneous leads (Fig. 2, *A*). If the stimulating electrode was not exactly over the bundle of His, the impulse entered the ventricular muscle at an abnormal site (via an abnormal pathway), and the resulting QRS complexes were grossly abnormal, as in ventricular extrasystoles or ventricular tachycardia. After the position of the electrode on the bundle of His was verified by normal QRS complexes in all leads, movement of the electrode as little as 1 mm. caused the ventricular complexes to become distinctly abnormal (Fig. 2, *B*).

In six of nine experiments, the position of the electrode on the bundle of His was demonstrated by the presence of normal QRS complexes in all leads. In five of these six instances, the position of the electrode was further verified by the fact that slight pressure applied to the electrode caused the development of complete heart block (Fig. 3); normal ventricular complexes again were recorded when the pressure was relieved and stimulation through the electrode resumed.

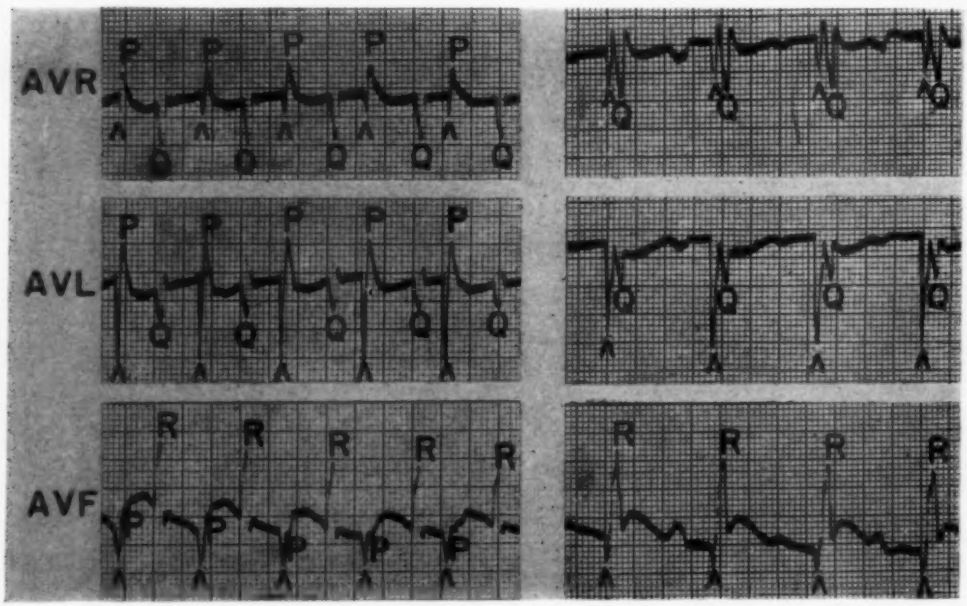

Fig. 4.—Simultaneous leads recorded at double speed (50 mm. per second): *A*, while heart is driven by electrical stimuli applied through the electrode near the A-V node; *B*, while the stimulating electrode is on the bundle of His.

Stim-QRS interval is approximately 1.15 second longer in *A* than in *B*, establishing that a delay in A-V conduction occurs between the head of the node and the bundle of His. Note that the QRS complexes are almost identical in the two tracings.

On one such occasion, a temporary right bundle branch block was first produced by pressure on the electrode, followed by a left bundle branch block after only slight movement of the electrode, followed in turn by complete heart block when the bundle of His was finally located. In three experiments, there was apparent failure to locate the bundle of His since normal QRS complexes were not obtained.

In each of the six successful experiments, the Stim-QRS interval in the electrocardiograms was considerably shorter when the stimulating electrode was on

the bundle of His than when the electrode was in the region of the A-V node. Hence, a delay in conduction occurred on the normal A-V conducting system somewhere between the head of the node and the bundle. Fig. 4 shows the results of a typical experiment; here the Stim-QRS interval was approximately 0.13 second shorter when stimuli were applied at the bundle of His than when the stimulating electrode was at or near the auricular portion of the A-V node.

Experiment 2.—Experiment 1 establishes that an impulse traversing the normal A-V conduction system is delayed between the head of the A-V node and the bundle of His. In order to determine the site of delay with greater precision,

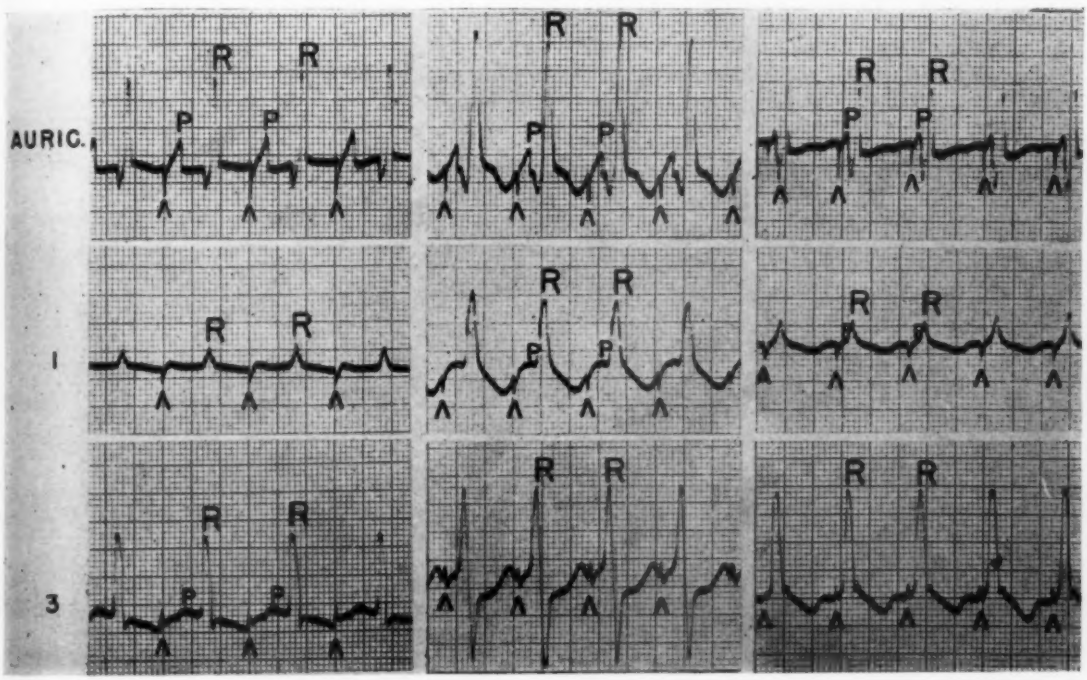

Fig. 5.—Simultaneous electrocardiograms recorded at double speed (50 mm. per second) while stimuli are administered through the electrode at various sites in the lower portion of the auricle and A-V node. *A*, Stimulating electrode is low in the auricle; Stim-QRS interval measures 0.14 second. *B*, Stimulating electrode is on the A-V node; Stim-QRS interval measures 0.08 second. *C*, Stimulating electrode is on the A-V node slightly caudad to electrode position *B*; Stim-QRS interval is 0.04 second. Hence, the normal delay in conduction must occur somewhere in the auricular portion of the A-V node.

electrocardiograms were recorded while a stimulating electrode was located at successively lower levels of the A-V node. As illustrated in Fig. 5, when the electrode was low in the auricles in the region of the A–V node, a Stim-QRS interval of 0.14 second was recorded (Fig. 5, *A*). When the electrode was moved slightly caudad, to a site in the auricular portion of the A-V node, a Stim-QRS interval of 0.08 second was inscribed (Fig. 5, *B*). When the electrode was moved slightly more caudad in the auricular portion of the node, the Stim-QRS interval was 0.04 second (Fig. 5, *C*). Therefore, the delay on the normal A-V conduction pathway must occur in the auricular portion of the A-V node.

DISCUSSION

While experiments 1 and 2 establish that the normal cardiac impulse is delayed in the auricular portion of the A-V node, our observations fail to show whether the delay consists of slow transmission or complete stoppage of the impulse. We cannot, therefore, confirm or deny Lewis' law of cardiac muscle from which he assumed slow transmission. However, Ashman's[8] observations against the latency theory provide support for the hypothesis that the delay in conduction in the auricular portion of the A-V node represents slow transmission rather than stoppage of the cardiac impulse.

An interesting incidental observation made during the present series of experiments is the production of complete heart block by compression of the auricular portion of the A-V node. On several occasions the Wolff-Parkinson-White syndrome or a nodal rhythm was produced by electrical stimulation of the auricular portion of the A-V node; increased pressure on the stimulating electrode in these instances frequently caused complete heart block (Fig. 6).

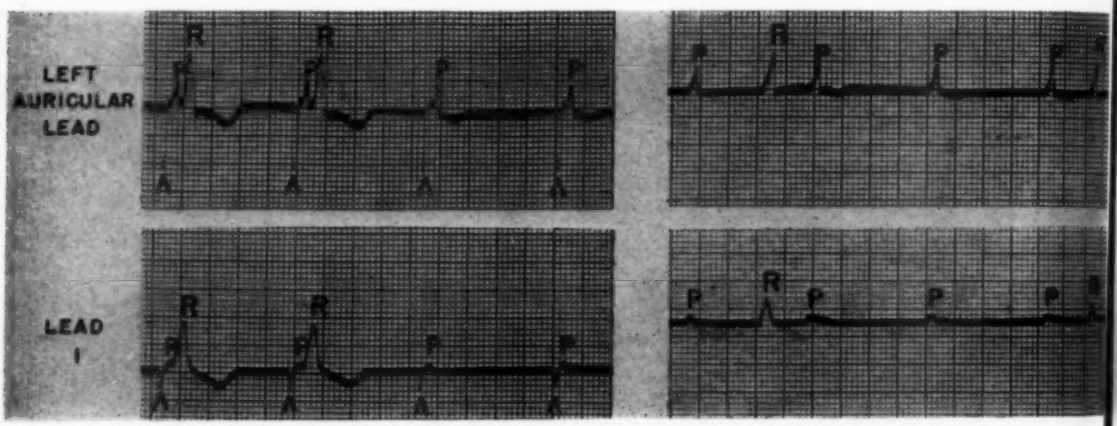

Fig. 6.—Simultaneous leads recorded at double speed (50 mm. per second) showing complete heart block produced by pressure on the electrode at the auricular portion of the A-V node.

A second by-product of the experiments is the demonstration of a ventricular tachycardia with narrow QRS complexes. When ventricular tachycardia was produced by stimulation of the bundle of His, the resulting QRS complexes were similar in configuration to those usually seen in supraventricular tachycardia. Ventricular tachycardia with narrow QRS complexes of the supraventricular type also has been produced in this laboratory by stimulation of the apex of the left ventricle (Fig. 7). This observation provides experimental evidence that ventricular tachycardia cannot be diagnosed from the shape of the QRS complex alone.

SUMMARY AND CONCLUSIONS

1. The two theories heretofore advanced to account for the major portion of the P-R interval in the normal electrocardiogram are reviewed. One theory

postulates slow transmission of the cardiac impulse in the A-V node; the other theory assumes a prolonged delay in conduction between the terminal endings of the A-V conducting system and the ventricular muscle. No direct evidence has been advanced in support of either theory.

2. In each of six animals, stimuli were applied successively to the A-V node and to the bundle of His while double speed electrocardiograms were recorded. The time interval between application of the stimulus and inscription of the Q S complex was greater when the A-V node was stimulated, demonstrating that the normal delay in A-V conduction occurs between the head of the node and the bundle of His.

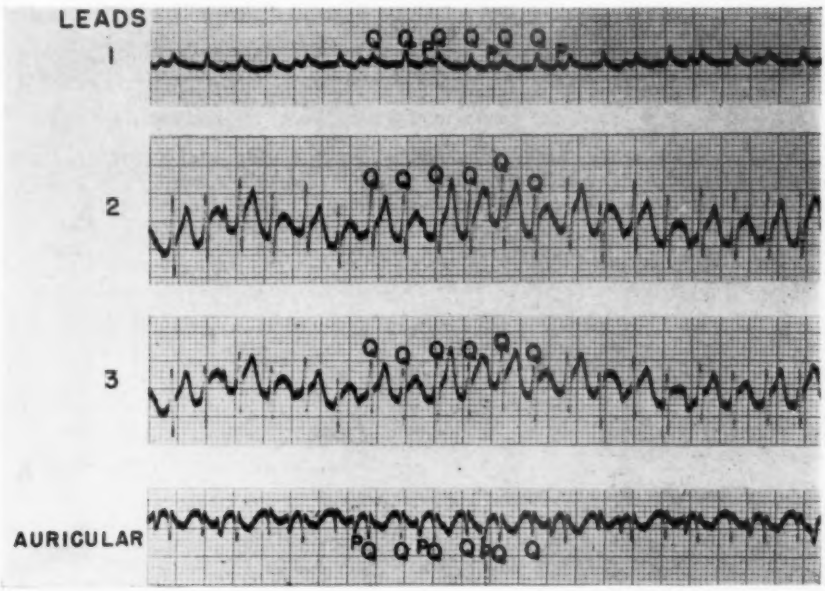

Fig. 7.—Simultaneous limb leads and direct auricular lead recorded at regular speed (25 mm. per second) showing narrow QRS complexes inscribed during ventricular tachycardia produced by electrical stimulation of a site at the apex of the left ventricle. The limb leads are identical with those of a supraventricular tachycardia; only in the direct auricular lead is the correct diagnosis revealed.

3. By comparing the time intervals between the application of the stimulus and the inscription of the QRS complex in tracings recorded during stimulation of successively lower levels of the A-V node, the normal delay in conduction was demonstrated to occur in the auricular portion of the node.

4. The Wolff-Parkinson-White electrocardiographic pattern may represent failure of the cardiac impulse to undergo the normal delay in the auricular portion of the A-V node, resulting in premature excitation of a ventricular focus.

5. Complete heart block can be produced by compression of the auricular portion of the A-V node.

6. Narrow QRS complexes of a type characteristic of supraventricular tachycardia may also occur in tachycardia of ventricular origin.

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SPATIAL VECTORCARDIOGRAPHY: RIGHT BUNDLE BRANCH BLOCK. VIII.

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THE patients selected for this discussion of the vectorcardiographic findings in right bundle branch block were those whose electrocardiograms fulfilled the following requirements: (1) a widened S wave in Lead I, 0.04 second or more, regardless of the voltage, and (2) any one of the following patterns in Leads V_1 or V_{R3}: rsR′, rsr′, rSr′s, qR, or an upright M-shaped complex. Both criteria were fulfilled in all cases but one. In this patient, the S wave in Lead I was of short duration (0.02 second), but the precordial leads gave definite evidence of conduction delay. Of the twenty cases selected from a series of forty-nine cases studied, there were five whose QRS duration was 0.11 second or less. These may be termed incomplete right bundle branch block. The remainder, fifteen cases, were considered to be instances of complete right bundle branch block. Of these latter cases, the QRS duration was 0.12 second in five, 0.13 second in three, 0.14 second in four, and 0.15, 0.16, and 0.17 second in one case each.

Electrocardiograms which display abnormalities of impulse conduction to the right ventricle are further divided into (1) the so-called classical and (2) the atypical (or Wilson) type of bundle branch block. The differentiation is based upon the appearance of the QRS complex in the standard leads. In the so-called classical right bundle branch block, Lead I consists of a small r wave and a deep, wide, slurred S wave followed by an elevated ST segment and an upright T wave. The reverse configuration may be seen in Lead III. The QRS duration is always in excess of 0.12 second. This type is very uncommon and only a single case is reported here. All of the remaining nineteen cases are of the so-called atypical variety. Wilson and associates[1] described the characteristics of this type of block as follows: (1) There is a prolonged QRS complex; (2) Lead I consists of a rapid, tall R wave and a broad, slurred S wave with an upright T wave, and (3) Lead III consists of a small q wave and a tall, slurred R wave with an inverted T wave. However, the variation in the shape of the QRS in the standard leads is considerable, and the only constant feature is the terminal abnormality which is manifested as a slurred, widened S wave in Lead I and left-sided chest leads and as an R′ or late R wave in Leads V_1 or V_{R3}.

The reason for the variety of patterns in atypical right bundle branch block is that only the terminal portion of the wave of accession is markedly affected.

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Therefore, the initial portion of the QRS complex up to the slurred S wave may take any normal form depending upon the spatial position of the main portion of the QRS SÊ loop or any abnormal form depending upon the presence and type of coexistent heart disease.

A subclassification of the nineteen cases of atypical right bundle branch block is then possible into those with known heart disease and those with no known heart disease. Of the former, three had left ventricular hypertrophy due to arterial hypertension, three had healed anterior infarctions, and five had myocardial damage resulting from coronary artery disease. It was, therefore, possible to observe the effects of the bundle branch block upon the spatial vectorcardiogram of those with various disease states and vice versa.

Finally, one case of transient or intermittent right bundle branch block of the complete, atypical variety was studied.

It will be noted that no case of right ventricular hypertrophy is included. In previous publications[2,3] it was demonstrated that the rSR′ complex, seen so commonly in patients with interatrial septal defects or mild pulmonary stenosis, was not a form of bundle branch block but rather a variation of the pattern resulting from hypertrophy of the right ventricle. Moreover, in the spatial vectorcardiograms of patients with right ventricular hypertrophy, no definite evidence of conduction delay was ever noted. Finally, a gradual transition, associated with increasing degrees of right ventricular systolic pressure, was found between those patients whose electrocardiograms showed the rsR′ complex and those whose electrocardiograms showed classical patterns of right ventricular hypertrophy.[3]

The theoretical problems of spatial vectorcardiography[4,5] and those particularly associated with the RSR′ configuration in right-sided chest leads[2] have been reviewed extensively in previous publications. The relationship of the horizontal plane vectorcardiogram to the unipolar chest leads has also been discussed previously.[5] The purpose of this communication is to describe the vectorcardiographic changes which were observed in one patient with transient atypical right bundle branch block, to present the variety of spatial forms and orientations recorded, and to present observations upon the effect of right bundle branch block on the spatial vectorcardiograms of patients with disease states.

The patients were all selected from the wards and clinics of the Mount Sinai Hospital. A Technicon vectorscope and electrocardiograph were utilized in the study. Electrode placement and technique have been described elsewhere.[4]

RESULTS

Transient Bundle Branch Block.—The electrocardiograms and spatial vectorcardiograms obtained in the patient with transient right bundle branch block will be presented first because they illustrate the alterations caused by this conduction abnormality upon a normal pattern. The patient was a 54-year-old white woman with marked arterial hypertension (230/120 mm. Hg) which was discovered on admission to the hospital for cholecystitis. Intermittent right bundle branch block was discovered in a routine electrocardiogram. It

was found possible to reproduce it by increasing the cardiac rate (through excitement or deep respiration).

In the electrocardiograms shown in Fig. 1, one normal and one abnormal beat are seen in each lead. The transition from normal conduction to right bundle branch block is always sharp with only a single "transitional" complex seen in the second beat in Leads $V_{4,5,6}$ (recorded simultaneously). Similarly, the return to normal conduction is a sharply defined event. The QRS duration increases from 0.09 second to 0.14 second. The conduction defect occurs when the heart rate increases from 60 to 65 beats per minute, with a return to normal with its slowing.

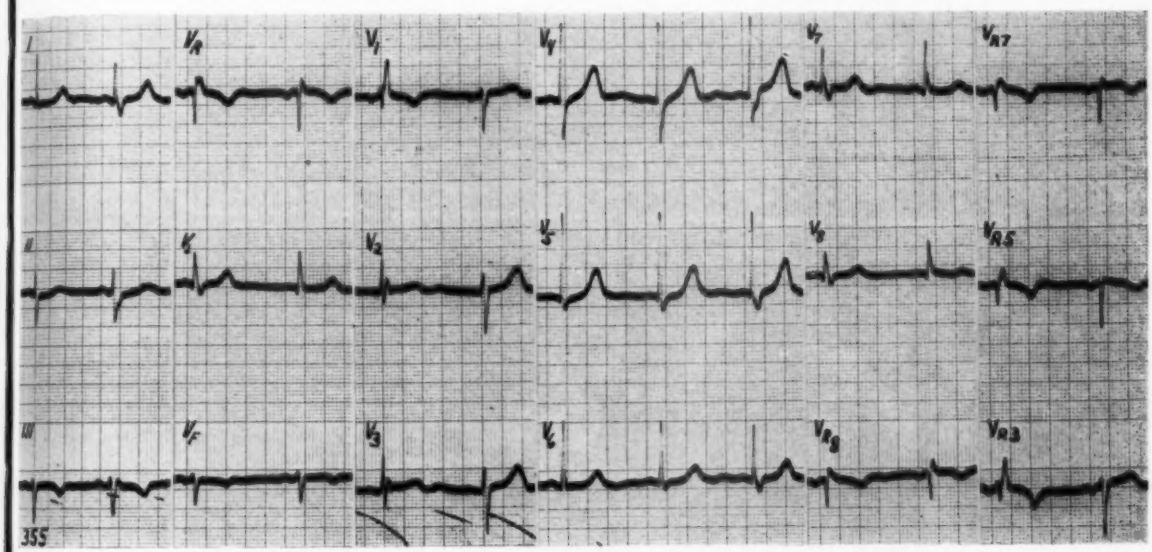


Fig. 1.—Transient right bundle branch block. Complexes exhibiting normal ventricular conduction are seen to alternate with those of right bundle branch block, with duration of the QRS complexes of 0.09 second and 0.14 second, respectively. In $V_{4,5,6}$ a transitional complex of partial right bundle branch block can be seen.

The alteration in the form of the QRS complexes in the beats with right bundle branch block in standard lead I consists of (1) diminution in the height of the R wave and (2) the appearance of a widened, slurred, shallow s wave. The Q-T interval is unchanged (0.48 second). The T wave, however, is of greater amplitude, and the total area under it is greater. In Lead III, an R′ wave appears, and the T wave is more deeply inverted. Lead V_R shows the development of a widened R wave and more deeply inverted T wave. In Leads V_{R5}, V_{R3}, V_1, V_2, and V_3, there is the appearance of a late, widened, slurred R′ wave. This is really the fundamental feature of the pattern. The T wave in V_{R3} is diphasic in the normal complexes and deeply inverted in the abnormal beats. Similarly, the upright T waves of the normal beats of V_1, V_2, and V_3 become either inverted or diphasic when abnormal conduction prevails. It also may be noted that the R wave of Leads V_2 and V_3 is taller in the complexes with right

bundle branch block than in those with normal conduction. All precordial leads taken beyond V_3 on the left side of the chest show the development of a slow, widened S wave with increasing height of the T waves. The vectorcardiograms obtained are shown in Fig. 2. Though numerous records were taken, only two patterns shown here were obtained. No intermediate forms could be distinguished.

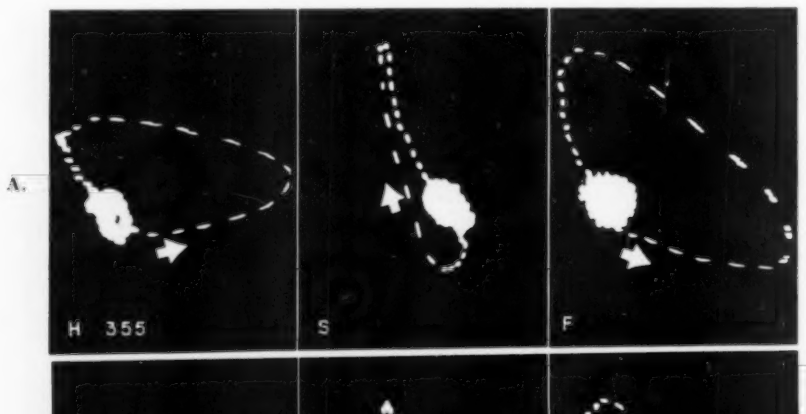


Fig. 2.—*A*, The spatial vectorcardiogram recorded when normal conduction prevailed is oriented markedly superiorly and posteriorly to the left. The T sÊ loop, being directed anteriorly and inferiorly, diverges more from the long axis of the QRS sÊ loop than found in normal individuals. *B*, When right bundle branch block occurs, the long axis of the QRS sÊ loop is directed more anteriorly. A new component appears consisting of a terminal, slowed, irregular appendage which is directed anteriorly and to the right. The T sÊ loop has shifted more than 100 degrees and is now directed posteriorly and to the left, opposite to the slow terminal appendage, the characteristic finding of atypical right bundle branch block.

The vectorcardiograms of Fig. 2,*A* may be taken as a representative of the normal adult pattern. The horizontal plane QRS SÊ loop is counterclockwise in its rotation, and its long axis lies to the left and slightly posterior. The T SÊ loop is small and is directed anteriorly and to the right. This divergence between the QRS axis and the T axis is more than normal, but the deviation of the T loop to the right is not sufficient to cause inversion of the T waves in V_5 and V_6. In the sagittal plane, the rotation of the QRS SÊ loop is clockwise; the loop is narrow and is directed upward and posterior. The T SÊ loop is directed anterior and downward. This deviation likewise suggests an abnormality and is probably the result of early left ventricular hypertrophy. In the frontal plane, the rotation of the QRS SÊ loop is counterclockwise, and the long

axis lies in the first quadrant of the triaxial system at about +20 degrees. The T SÊ loop is very small, and its characteristics cannot be ascertained with any certainty. The spatial reconstruction of the loop from its projection onto the three planes would show that the general contours are smooth and rounded. There is a slow invasion period, a middle segment of rapid angular velocity, and a slowed terminal phase. This is determined from the close proximity of the time interruptions during the slow phases and the wide spaces between them during the period of rapid angular velocity.

The vectorcardiogram shown in Fig. 2,*B* is characteristic of atypical right bundle branch block. The changes are marked in all the planes. In the horizontal plane (*H*), the rotation of the QRS SÊ loop is still counterclockwise, but the following changes have taken place: (1) The centrifugal limb (outgoing) is directed more anteriorly; (2) the long axis of the loop has shifted anteriorly about 20 degrees; (3) the posterior limb does not extend as far posteriorly; (4) a new component has appeared which consists of a terminal, slowed, irregular appendage which is directed anteriorly and to the right; and (5) the T SÊ loop is greater in size and has shifted more than 100 degrees, being directed now to the left and posteriorly.

These changes in the spatial vectorcardiogram explain the changes noted in the electrocardiogram. The increased duration of the QRS complex is entirely the result of prolongation of the terminal period of accession. The late, widened, slurred R′ wave in V_{R5}, V_{R3}, V_1, V_2, and V_3 is a projection onto these leads of this terminal portion of the loop which is slow, irregular, and directed to the right and anteriorly. The slow S wave in Leads V_4, V_5, V_6, and V_7 is the result of the negative projection of this same segment. The increased amplitude of the R waves in V_2 and V_3 is the result of the more anterior course of the centrifugal limb. The fact that the T waves of Leads V_1, V_2, and V_3 are changed from upright to inverted or diphasic is explained by the shift of the axis of the T SÊ loop posteriorly and to the left. This also accounts for the increased height of the upright T waves in Leads V_5 and V_6. The alterations in the sagittal projection (*S*) of the cardiac vector reflect the ones mentioned in the horizontal plane. The initial segment is directed downward and slightly more anteriorly. The anterior displacement of the terminal segment is well shown as well as its slow, irregular character. In the frontal plane (*F*) the loop does not extend as far to the left as in the normal beats. The slow, irregular terminal loop which extends to the right and downward is again evident. The T SÊ loop is directed to the left and slightly upward. These changes explain well the decreased height of the R wave in Lead I, the slurred S wave in Lead I, the R′ wave in Lead III, and the increased area and amplitude of the T wave in Lead I and more deep inversion in Leads III and V_R.

From the spatial vectorcardiogram, all alterations in the electrocardiogram can be explained and some insight can be gained into the over-all pattern of the alterations in the electrical field which are brought about because of right bundle branch block.

Irreversible Right Bundle Branch Block.—In classifying these vectorcardiographic patterns for descriptive purposes, it was found that there were only two

significant groupings. The first group separated the one patient with "classical" right bundle branch block from the remainder. The secondary grouping of the "atypical" bundle branch block patterns was then made on the basis of associated cardiac pathology. The duration of the QRS interval did not correlate with any specific type of vectorcardiographic pattern.

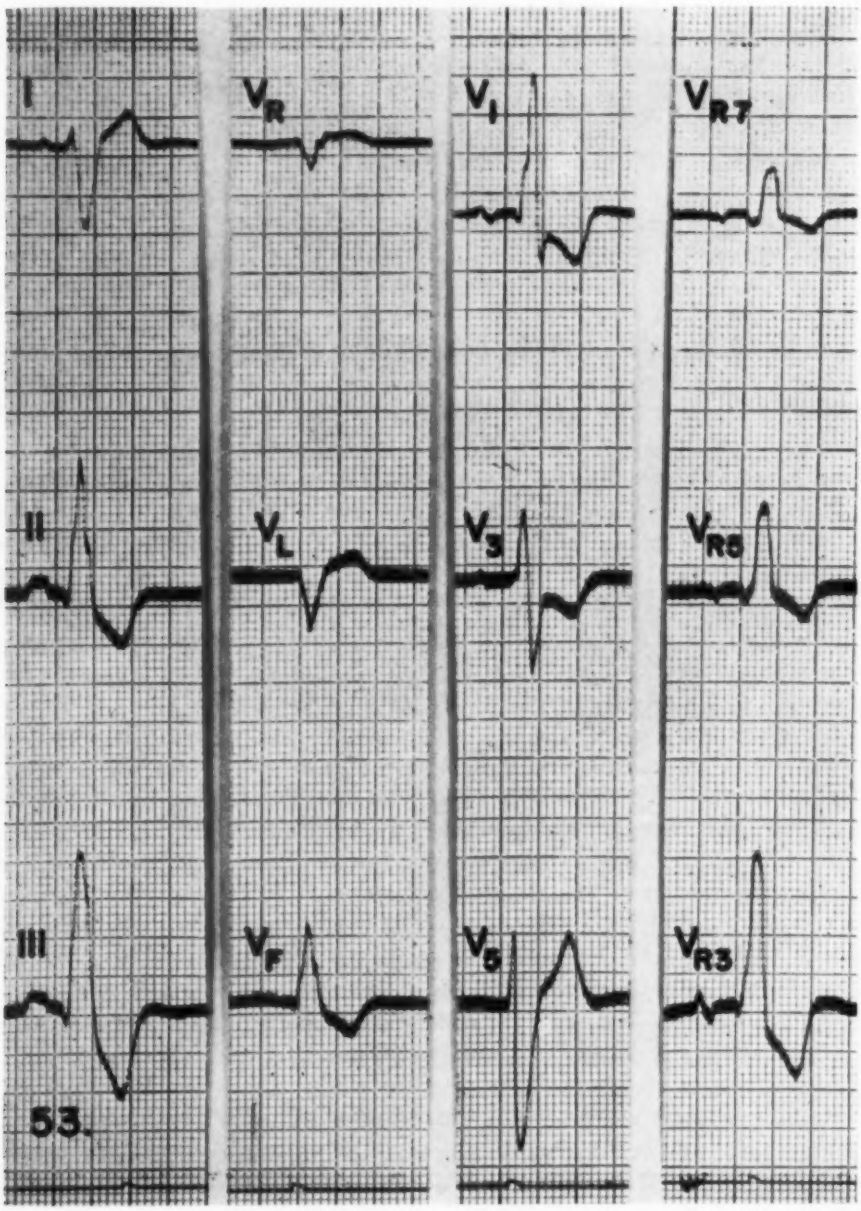


Fig. 3A.—Classical right bundle branch block (so-called rare type). The electrocardiogram shows a marked right axis deviation and widening of the QRS complexes to 0.16 second. qR complexes are recorded in right-sided chest leads with discordant deviation of the ST segments and T waves.

Classical right bundle branch block is quite uncommon. The characteristic electrocardiogram is shown in Fig. 3,*A*. Lead I consists of a small r and a deep, wide S wave with an upright T wave and an elevated ST segment. Lead III consists of a small q wave, a tall, wide R wave, an inverted T wave, and a depressed ST segment. The precordial leads from V_{R7} to V_1 show a qR complex with an inverted T wave. The left-sided precordial leads consist of an rS complex with an upright T wave. The vectorcardiogram shown in Fig. 3,*B* consists of a QRS SÊ loop whose long axis points toward +120 degrees. The direction of rotation is clockwise, and the time markers are very closely spaced throughout, with numerous small irregularities suggesting a slow, irregular progress of the wave of accession. The loop is not closed because the terminal limb passes above and slightly to the left of the isoelectric center. This results in ST segment deviations, positive in Lead I and negative in Leads II, III, and V_F. The T SÊ loop is discordant to the QRS SÊ loop. This pattern appears like the mirror image of what has been observed in left bundle branch block.

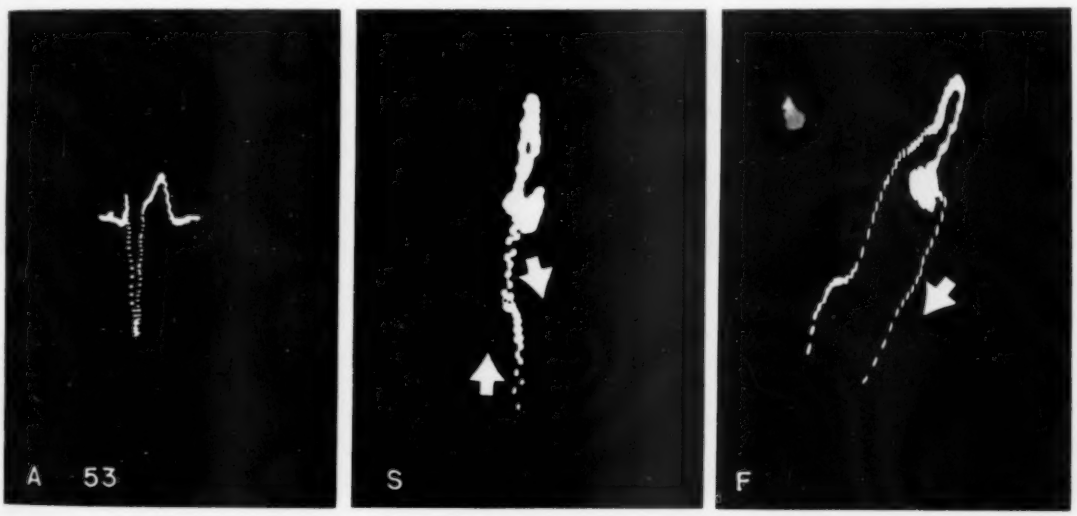
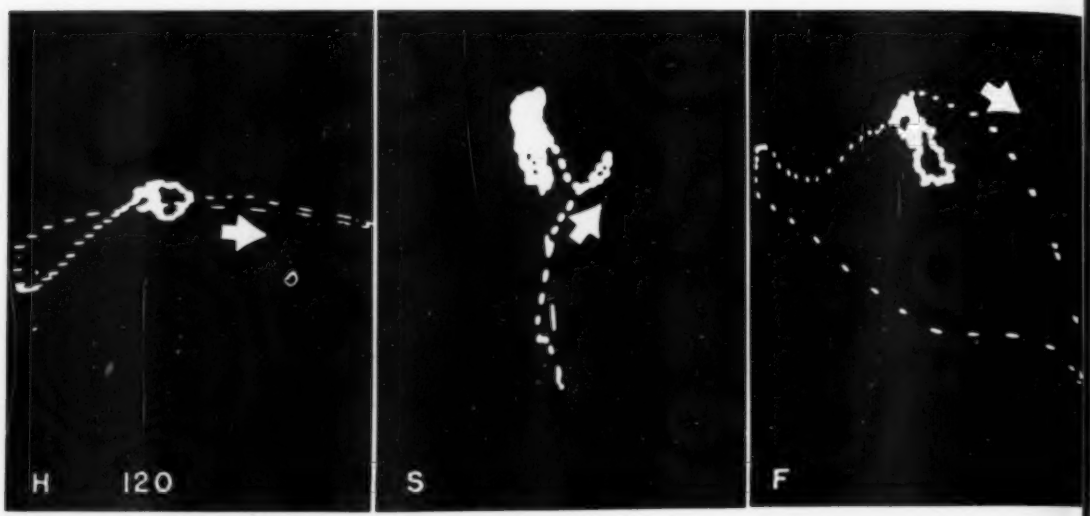


Fig. 3*B*.—The spatial vectorcardiogram is oriented right, inferiorly, and anteriorly with a clockwise rotation of the QRS sÊ loop in the frontal plane projection. The QRS sÊ loop is seen not to return to its point of origin (open loop). The T sÊ loop is in discordant position to the QRS sÊ loop, and the ST vector is directed to the left and superiorly.

The remaining nineteen cases were divided into (A) those without known heart disease, (B) those with hypertrophy of the left ventricle, (C) those with diffuse heart disease, either arteriosclerotic or thyrotoxic, and (D) those with myocardial infarctions.

A. No heart disease: The vectorcardiograms shown in Figs. 4,*A* and 5 are representative of the variety of patterns seen in this group. Right bundle branch block of the so-called atypical variety causes only minor alterations in the form of the main portion of the QRS SÊ vector loop. This is well seen in the patient with transient right bundle branch block. The slow, terminal irregular wave of the vectorcardiogram may coexist with any of the variety of normal

major QRS SÊ loops described previously.[5] In Fig. 5,*A* and *C*, the rotation is counterclockwise in the frontal plane, and the long axis is between 0 and +10 degrees, resulting in left axis deviation in standard leads, whereas in *B* and Fig. 4,*A* the rotation is clockwise and the long axis is about +50 degrees, resulting in a tendency toward right axis deviation. Variations in the terminal segment are also seen. The least abnormality is seen in Fig. 5,*A* (203), where there is



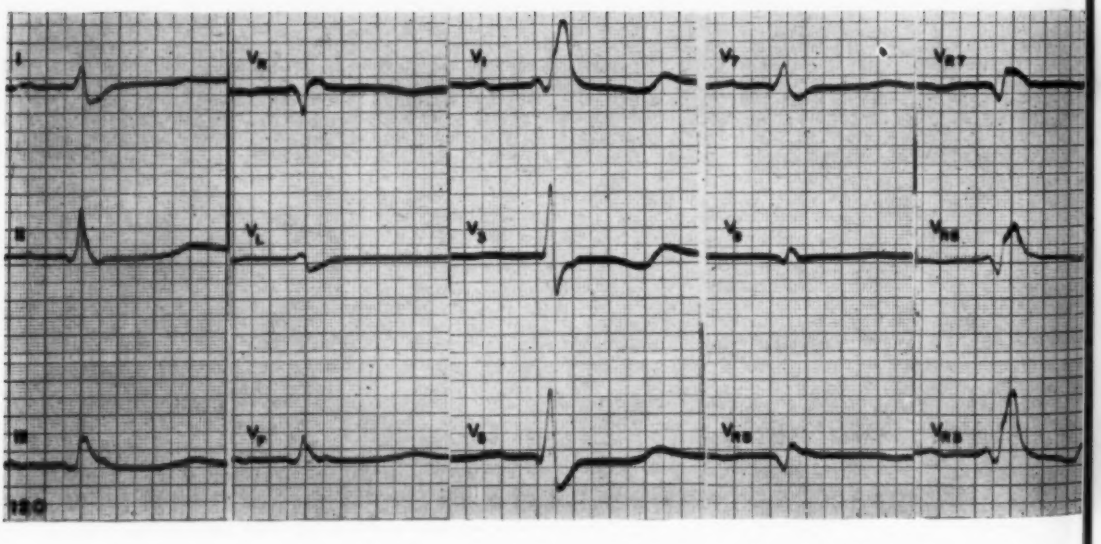


Fig. 4.—*A*, Atypical right bundle branch block in the absence of clinical heart disease. The spatial vectorcardiogram is oriented to the left and inferiorly. The slow terminal appendage is directed to the right and anteriorly. *B*, The electrocardiogram (recorded at 10 cm. per second) reveals an rsR′ configuration of the QRS complexes in V_{R5}, V_{R3}, and V_1.

only a very small, terminal, slowed loop. This is just large enough to produce a small rsr′s complex in V_1 and an s wave in Lead I. The remaining patterns show greater degrees of change. In all, however, the terminal portion of the loop is directed anteriorly (seen clearly in the sagittal and horizontal planes) and to the right (seen clearly in the frontal and horizontal planes). In the spatial vectorcardiogram shown in Fig. 5,*C* (151), it is observed that the centripetal limb runs anterior to the centrifugal one, thus forming a clockwise loop.

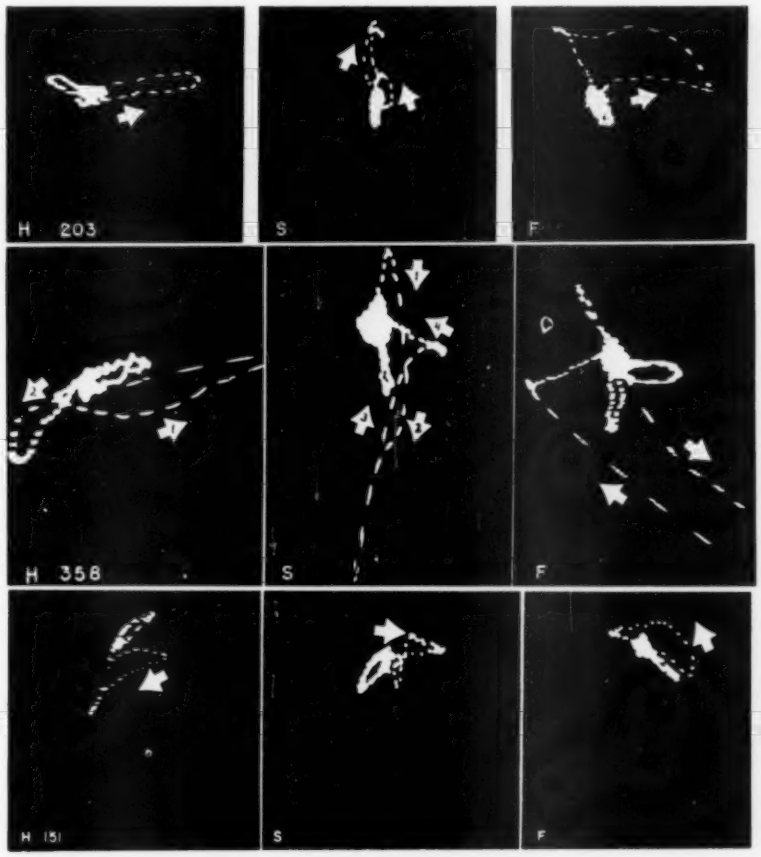
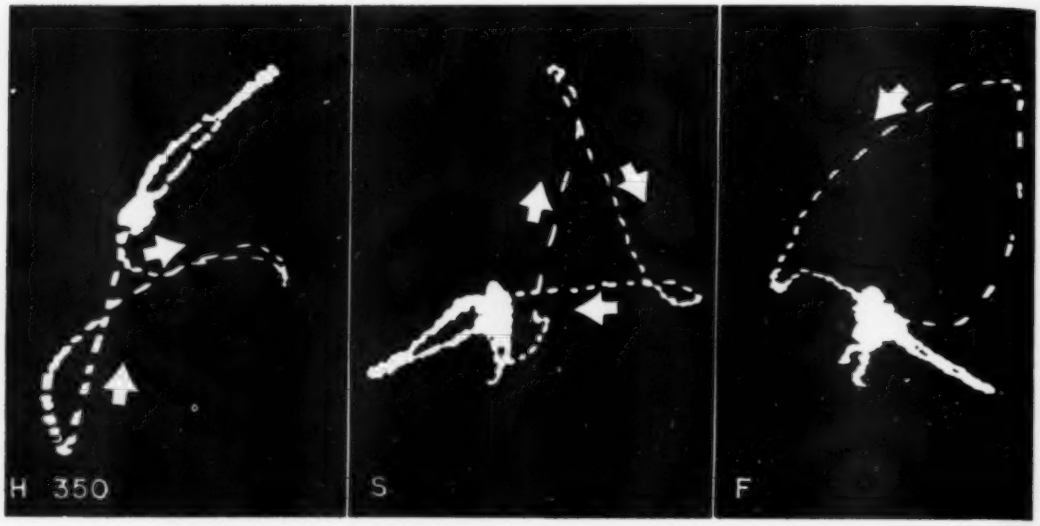


Fig. 5.—Spatial vectorcardiograms of atypical right bundle branch block of patients without clinical heart disease. *A* (203), The orientation of the QRS sÊ loop is to the left and superiorly, its terminal appendage to the right, superiorly and slightly posteriorly, and that of its T sÊ loop inferiorly. *B* (358), The QRS sÊ loop is oriented to the left and inferiorly, its terminal appendage to the right, inferiorly and anteriorly, and its T sÊ loop to the left and slightly posteriorly. *C* (151), The QRS sÊ loop is oriented to the left, superiorly and anteriorly, its terminal appendage to the right, anteriorly and slightly superiorly, and its T sÊ loop to the right, posteriorly and inferiorly.

The explanation of the anterior position of this centripetal limb is probably to be found in the balance of forces arising in the left posterior and right anterior segments of the heart at the time of the delayed onset of activity in the right ventricle. It does not seem to represent a fundamental difference in mechanism from the others. This difference in spatial vector pathway is not discernible by electrocardiography.

A.



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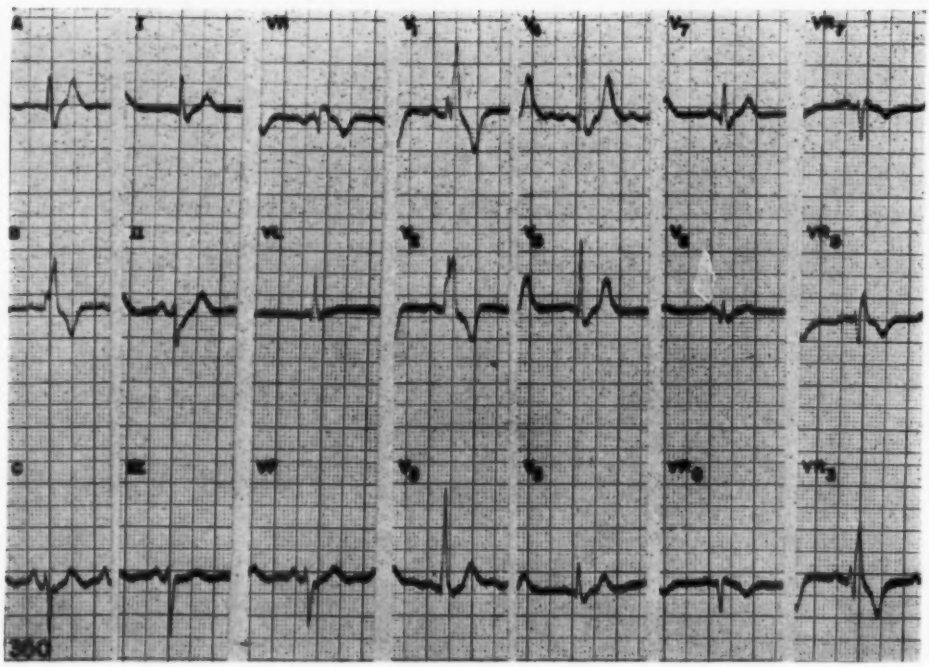

Fig. 6.—Atypical right bundle branch block in the presence of left ventricular hypertrophy. *A*, The spatial vectorcardiogram is oriented to the left, markedly superiorly and anteriorly, its terminal appendage to the right, anteriorly and slightly superiorly, and its T sÊ loop to the left, posteriorly and inferiorly, opposite to the terminal appendage. *B*, The electrocardiogram reveals atypical right bundle branch block. Note the upright T waves in Lead I and left-sided chest leads in the presence of left ventricular hypertrophy.

B. Left ventricular hypertrophy: The three vectorcardiograms shown in Figs. 6,*A* and 7 illustrate several features of the patterns formed by left ventricular hypertrophy combined with right bundle branch block. All three patients had arterial hypertension with left ventricular enlargement. It is evident that the existence of hypertrophy has not altered the configuration or orientation of the slow, terminal loop. Here, as well as in those without heart disease, it is slow, irregular, and directed anteriorly and to the right. However, the existence of the right bundle branch block has altered the relationship between the QRS SÊ loop and the T SÊ loop. In the frontal plane vectorcardiogram of Figs. 6 and 7,*A* and *B*, it is seen that the T SÊ loop points downward and to the left. This results in upright T waves in standard leads I and III instead of an anticipated inverted T in Lead I if left ventricular preponderance would exist alone.

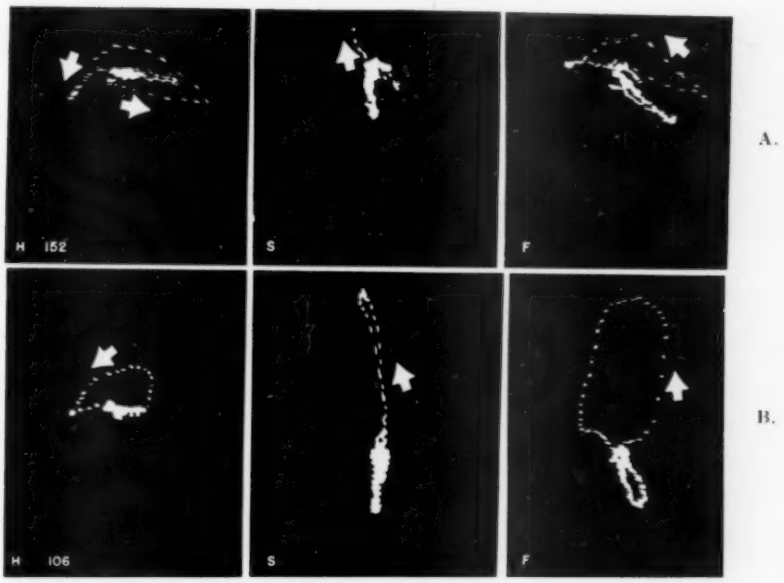

Fig. 7.—Atypical right bundle branch block in the presence of left ventricular hypertrophy. *A* (152), The QRS sÊ loop is oriented to the left and superiorly, its terminal appendage to the right and anteriorly, and its T sÊ loop to the left and inferiorly. *B* (106), Note the marked superior and slightly posterior orientation of the QRS sÊ loop. The terminal appendage is oriented to the right, somewhat anteriorly and superiorly, while its T sÊ loop is directed to the left and inferiorly.

The horizontal plane projection shows clearly the terminal abnormality associated with right bundle branch block in all three cases. However, in Fig. 7,*A* and *B*, this part of the loop is directed to the right, but laterally, rather than anteriorly. This results in an rSr′ type of complex in Lead V_1 rather than the rsR′ seen in the other two.

This chief point of interest lies again in the relationship between the QRS SÊ loop axis and the T SÊ loop axis. In all three vectorcardiograms, the T loop axis is directed opposite to that of the terminal portion of the loop rather than opposite to that of the axis of the major portion of the ventricular loop.

This results in downwardly directed T waves in precordial leads V_1 and V_2 and upright T waves in V_3 through V_7. This relationship of the QRS to T complex is seen in right bundle branch block and is opposite to that of left ventricular hypertrophy. Therefore, the electrocardiographic diagnosis of left

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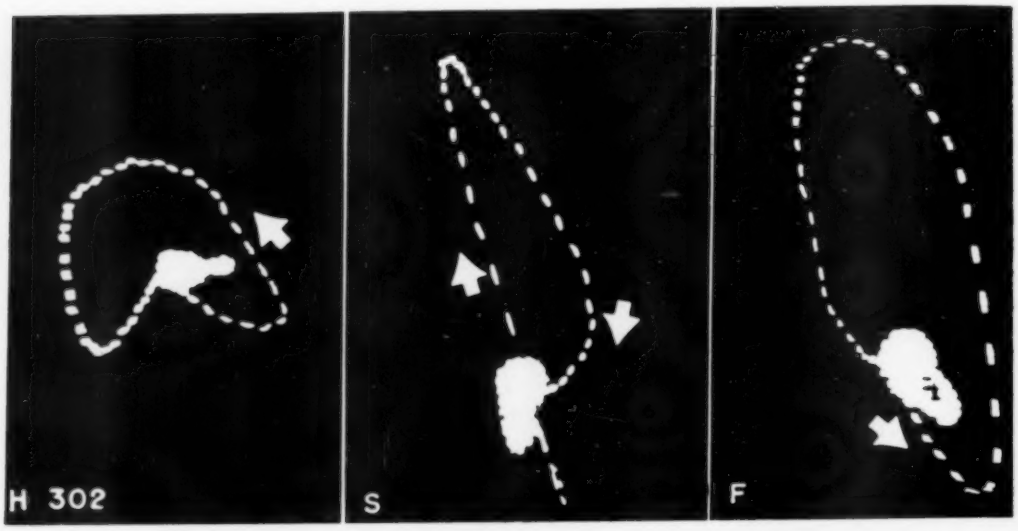

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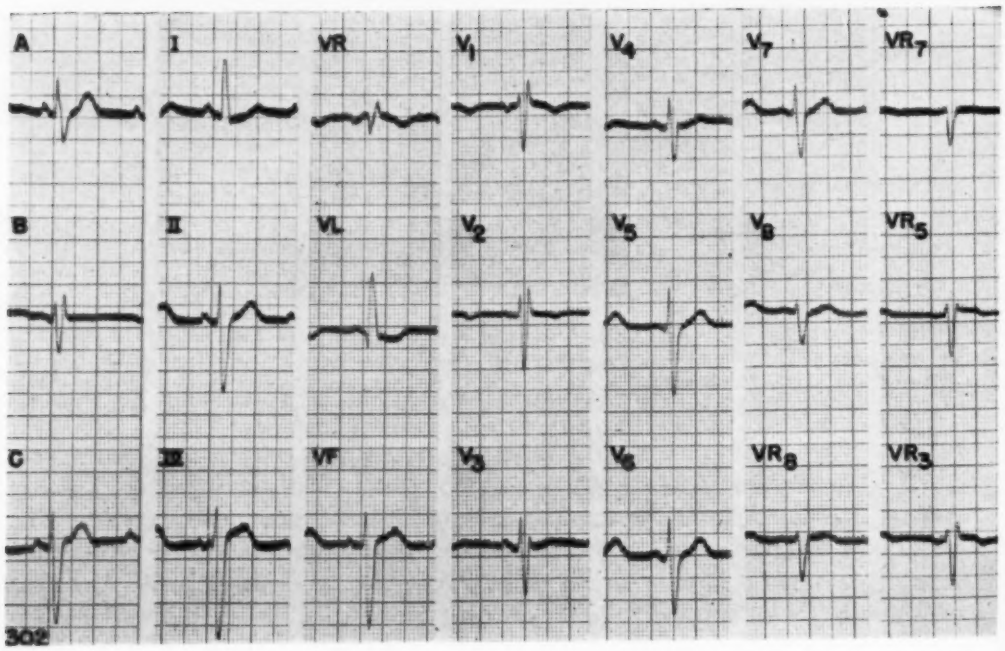

Fig. 8.—Atypical right bundle branch block in the presence of myocardial damage. *A*, The spatial vectorcardiogram reveals a bizarre QRS sÊ loop with a terminal appendage right anteriorly and somewhat superiorly. The T sÊ loop is in an almost opposite direction to the terminal appendage. *B*, The electrocardiogram shows upright T waves in Lead I and left-sided chest leads.

ventricular hypertrophy could not be made in any of these three patients by applying conventional standards. The diagnosis, however, can be made with certainty from the configuration of the QRS SÊ loop of the vectorcardiogram without regard to its relationship to the T SÊ loop. The T-wave position observed in these three cases is consistent with the direction of the T-wave alterations observed in the patient with transient bundle branch block. Therefore, it is apparent that the presence of right bundle branch block does mask T waves and ST alterations by virtue of the alterations in gradient. This is shown well in a tracing published by Barker and Valencia.[7] In their tracing, a diphasic T wave was present in V_6 during normal conduction, becoming upright during periods of right bundle branch block.

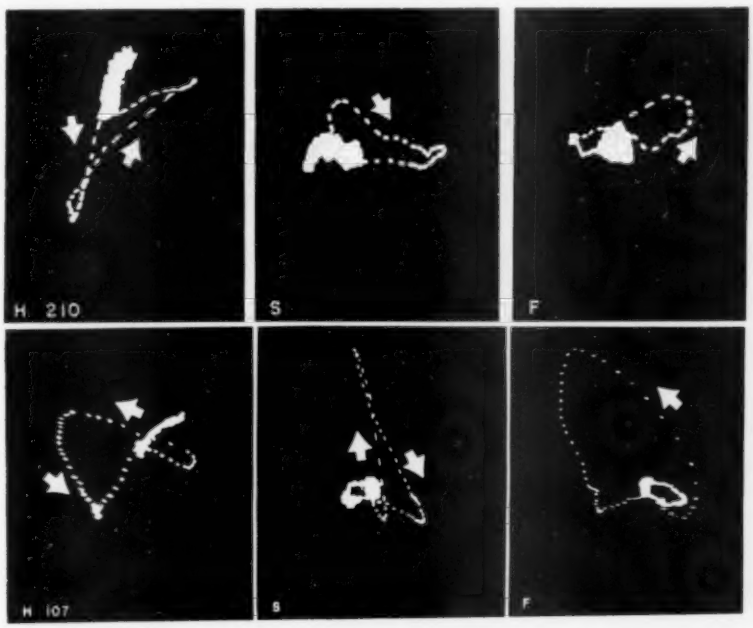

Fig. 9.—Atypical right bundle branch block in the presence of myocardial damage. *A* (210), The QRS sÊ loop is abnormal. The terminal appendage is oriented to the right and anteriorly. (In the horizontal projection the arrows should be read in a reversed direction.) *B* (107), The QRS sÊ loop is of bizarre configuration, with its terminal appendage oriented to the right and anteriorly.

C. Heart disease with diffuse myocardial involvement: This group broadly covers patients with coronary artery disease who have had no specific myocardial infarctions and others with heart failure from other causes. The three vectorcardiograms shown in Figs. 8,*A* and 9 are representative of this group. In all, we see the slow, irregular, terminal segment of the QRS SÊ loop which marks the presence of right bundle branch block. However, the major portion of the QRS SÊ loop differs widely in all cases. It is not within the scope of this paper to discuss the nature of these loops but simply to point out that they are markedly abnormal in one or many features in addition to the presence of the right bundle branch block. The T SÊ loop points in a direction opposite to that of the termina-

portion of the QRS SÊ loop, more or less without regard to the features of the major portion of the loop. This, as in the patients with left ventricular hypertrophy, causes the appearance of upright T waves in Lead I and in Leads V_5 and V_6. Since the electrocardiographic diagnosis of myocardial damage is

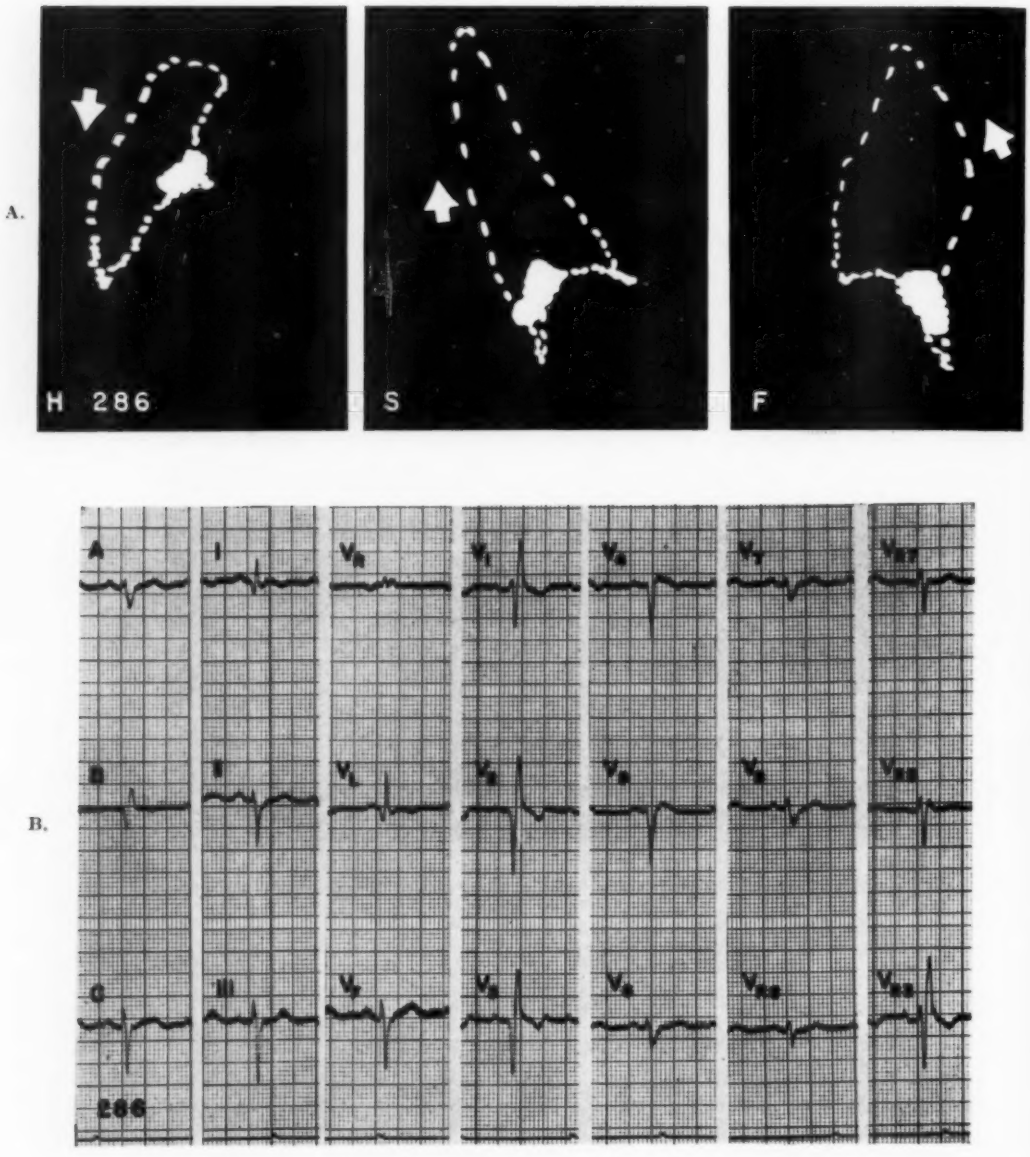

Fig. 10.—Atypical right bundle branch block in the presence of localized anterior wall infarction. *A*, In the spatial vectorcardiogram the initial posterior direction of the QRS sÊ loop indicates the presence of an "infarction vector" anteriorly, having displaced the loop posteriorly. The terminal appendage is directed anteriorly and to the right with the T sÊ loop oriented almost in the opposite direction. *B*, The electrocardiogram reveals a localized anterior wall infarction (Q waves in V_2 and V_3).

based chiefly upon the finding of inverted T waves in these same leads, considerable difficulty is usually experienced in making the diagnosis of myocardial damage in the presence of right bundle branch block. However, the diagnosis usually can be made from the configuration of the QRS SÊ loop of the vectorcardiogram alone. This is true because the electrocardiographic diagnosis depends upon the observation of an alteration of gradient while the vectorcardiographic diagnosis may rest upon alteration of the QRS SÊ or T SÊ loops separately.

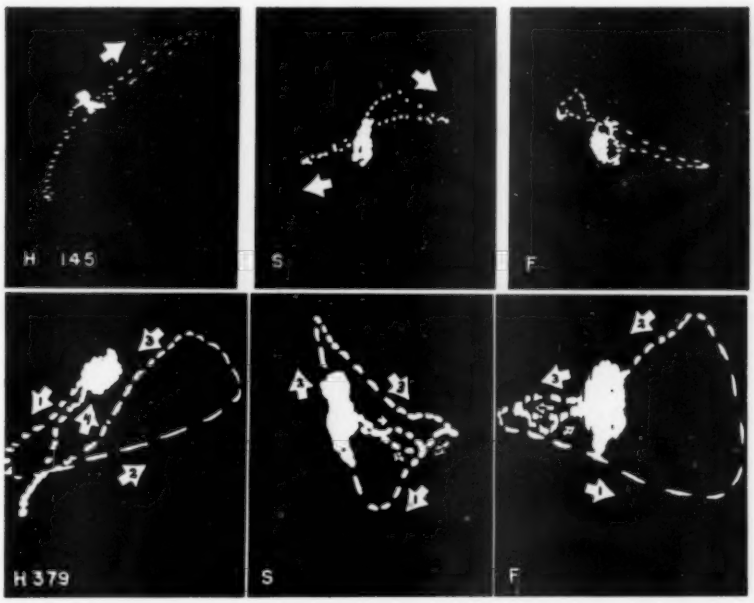

Fig. 11.—Atypical right bundle branch block in the presence of myocardial infarction. *A* (145), Anteroseptal infarction. The septal vector, normally directed to the right and anteriorly, is absent. The terminal appendage is directed anteriorly and to the right. The T sÊ loop is directed inferiorly and to the right. *B* (379), Posterolateral infarction. The centrifugal part of the QRS sÊ loop is markedly displaced anteriorly and to the right, indicating the presence of an "infarction vector" left posteriorly directed right anteriorly and displacing the loop in that direction. The terminal appendage is directed right anteriorly and the T sÊ loop inferiorly. Doubtless, additional factors influence the resultant direction of the T sÊ loop with a somewhat different behavior in comparison to spatial vectorcardiograms without infarction.

D. Myocardial infarction: It has been clear since the early work of Wilson[1] that it is possible to make a diagnosis of myocardial infarction in the presence of right bundle branch block. The three vectorcardiograms shown in Figs. 10,*A* and 11 are from patients who have had known myocardial infarctions. The alterations of the QRS SÊ loops which result from infarctions of specific types have been presented in a previous paper.[8] The presence of right bundle branch block contributes only the familiar terminal, slow, irregular portion of the QRS SÊ loop.

SUMMARY

The vectorcardiographic patterns and characteristics of right bundle branch block may be summarized as follows:

1. "Classical" right bundle branch block is associated with a QRS SÊ loop inscribed in the right, lower, anterior octant. The progress of the wave of accession is slow, and the time markers are closely spaced throughout the QRS SÊ loop. There is a positive ST vector directed upward, posterior, and to the left. The T SÊ loop is discordant. It points upward, backward, and to the left. Instances of this type of right bundle branch block are rare.

2. Atypical right bundle branch block is characterized by alteration chiefly of the terminal portion of the QRS SÊ loop. This terminal portion is increased in duration, slow and irregular in contour, and invariably directed to the right and anteriorly, to a greater or lesser extent. This terminal portion of the QRS SÊ loop produces the slow, widened S wave of Lead I and the R′ or late R wave of Lead V_1. This terminal abnormality may coexist with any normal or pathological variety of the QRS SÊ loop. The study of a case of transient, atypical complete right bundle branch block revealed that the major portion of the QRS SÊ loop is also affected by the presence of the abnormal conduction, though only to a minor extent. However, the fact that some change is produced in the initial portion of the QRS SÊ loop indicates that the lack of contribution of right ventricular electromotor force to the entire QRS cycle is detectable although of small quantity. This might be considered as evidence that this type of block is true bundle branch block and not merely a "focal block"[9] of the Purkinje system or a local abnormality of muscular conduction in the crista terminalis.

It was further observed that the long axis of the T SÊ loop shifted to the left and posteriorly by more than 100 degrees. The significance of the T SÊ loop shift was shown clearly in the patients with marked left ventricular hypertrophy or myocardial damage. The electrocardiographic diagnosis of both of these conditions depends greatly upon evidence of an altered gradient producing inverted T waves in Leads I and V_5 or V_6. That the T-wave change due to right bundle branch block alone would obscure such a diagnostic criterion was suspected from the alteration seen in the patient with transient block and was confirmed in the patients with left ventricular hypertrophy and myocardial damage associated with right bundle branch block. In all of them, T waves were upright in Leads I and V_5 and V_6. The diagnosis of myocardial damage, myocardial infarction, and left ventricular hypertrophy, however, could be made from the configuration of the QRS SÊ loop alone.

CONCLUSIONS

1. The spatial vectorcardiograms associated with right bundle branch block in patients without heart disease and with heart disease have been described.

2. The value of the vectorcardiogram in distinguishing between those patients with conduction abnormality and no heart disease and those with coexistent left ventricular hypertrophy or myocardial damage or infarction has been demonstrated.

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BLOOD PRESSURE REDUCTION TO A SELECTED LEVEL BY CONTINUOUS INJECTION OF METHONIUM HALIDES (C5 AND C6) AND THE USE OF AN ELECTRICALLY OPERATED SYRINGE

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DUNEDIN, NEW ZEALAND

STUDY of the pharmacology of quaternary ammonium bases began with Crum-Brown and Fraser[1] in 1868. Burn and Dale,[2] in 1915, showed that tetraethylammonium chloride has the capacity to block autonomic ganglia without appreciable nicotine-like initial stimulation. In 1948, Barlow and Ing,[3] interested in the curare-like actions of quaternary ammonium compounds, were led to synthesize chemical relatives of tetramethyl- and tetraethylammonium chloride in which two quaternary nitrogen groups were separated by a chain of CH_2 groups. The decamethonium salt (C10), with ten CH_2 groups, had a strong curare-like action, whereas pentamethonium (bromide) (C5) and hexamethonium (iodide) (C6) were shown by Paton and Zaimis,[4] in 1949, to block autonomic ganglia. Organe, Paton, and Zaimis[5] and Arnold and Rosenheim[6] showed that in man C5 by intravenous or intramuscular injection produces similar effects to tetraethylammonium chloride but acts in smaller doses. They reported that C5 leads to a fall of blood pressure which is more evident in the erect posture, the blood pressure fall being associated with pulse acceleration. Observations by Arnold, Goetz, and Rosenheim,[7] using a finger plethysmograph, indicated an increased flow through the fingers following intravenous injection. Burt and Graham[8] confirmed the results of Rosenheim and co-workers.[7] They reported rises in temperature, particularly in the leg and to a smaller degree in the arm, and noted also that blood pressure changes are much influenced by posture. Restall and Smirk[9] confirmed the effect of posture in hypertensive patients treated with C5 or C6 and noted that, with the patient seated, intravenous injections of 5 to 15 mg. led to falls of 1 to 6 cm. of water pressure in the arm and neck veins and to an increase in leg volume as measured plethysmographically. It seems that a part of the fall of blood pressure is due to dilatation of blood vessels in dependent parts, sometimes with decreased filling of the heart. The substances, while they act, perform a pharmacological sympathectomy. It was found also that with pentamethonium or hexamethonium halides the patient's arterial pressure could be lowered and held well below the basal blood pressure as determined by methods described by Alam and Smirk,[10] Smirk,[11] and Kilpatrick.[12]

With initial subcutaneous injections of 15 to 25 mg. in the sitting posture cardiac acceleration was a usual concomitant of blood pressure fall, but in patients

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habituated to the drug subcutaneous injections of 100 mg. or more may be given and systolic falls of 80 mm. Hg, with diastolic falls of 30 mm. Hg, may occur with little effect on the heart rate and without adverse subjective manifestations.

Salt-poor diets, providing a daily intake of 0.2 Gm. of sodium, and the Kempner diet enhance the action of methonium salts so that, under comparable conditions, one-half or one-third of the original dose now produces a full effect (Restall and Smirk[9]). Dangerous reactions may occur from ignorance of the effect of a salt-poor regime. Undue blood pressure lowering, for example, may induce prolonged anginal attacks in patients with coronary disease. Neo-Synephrine Hydrochloride, 0.5 c.c. of a 1 per cent solution intramuscularly, repeated if needed, proved a valuable means of restoring the blood pressure level.

For the purposes of treatment a useful degree of control over the level of the blood pressure in arterial hypertension may be obtained by two or three subcutaneous injections daily of the halogen salts of pentamethonium or hexamethonium. Initial trials showed a surprising clinical improvement in fifty-three hypertensive patients treated with these substances (Restall and Smirk,[9] Alstad and Smirk,[13] and Smirk[14,15]). There has been insufficient time to allow any comments on long-term results, but, on the basis of fourteen months' experience, it is already evident that with the blood pressure reduced effectively disappearance or striking reduction of papilledema, retinal edema, retinal hemorrhages, and some soft exudates is a usual result in the early months of treatment. Headaches disappear early; there is commonly a decrease in breathlessness on exertion; on occasion the heart size has been reduced; and in several instances the electrocardiogram has become more normal. Eventually patients inject themselves, and a number have returned to gainful employment. Accurate control of dosage is at least as important as in insulin treatment of diabetes mellitus.

Observations by the previously mentioned authors[9,13,14,15] on 130 high blood pressure patients of various types included patients with fixed and labile types of essential hypertension, malignant hypertension, hypertension remaining or recurring after sympathectomy, and the hypertensions of chronic nephritis, nonnephritic renal damage, and acute pregnancy toxemia, and the hypertension which remains after pregnancy toxemia. The blood pressure could be lowered in all these patients during the action of the drug irrespective of pathogenesis, and in most severe hypertensive patients systolic pressure decreases of 60 mm. Hg or more and a smaller lowering of the diastolic pressure could be effected without causing other than minor symptoms. In a few cases the degree of blood pressure reduction was inadequate, for example, 24 mm. in the systolic and 6 mm. in the diastolic pressure. Most of these patients had a fixed hypertension from advanced chronic nephritis. In other patients reductions of 120 mm. Hg in the systolic pressure have been made, sometimes without discomfort. From our initial experience it would seem that effective blood pressure reduction without important symptoms is possible in most types of high blood pressure. With two or three subcutaneous injections daily the troughs of the blood pressure falls occur usually in the course of the hour following injection, and the pressure gradually returns to its original high level over the next three or four hours (Fig. 1). Oral administration is possible but is less reliable and requires larger doses.

As far as we are aware up to the time of writing, only three further reports (Turner,[16] Saville,[17] and Campbell and Robertson[18]) have been published on this use of methonium salts. No definite conclusions were reached by the first two authors, but Saville[17] was hopeful that methonium salts would find a place in the treatment of hypertension. Both of these workers used relatively large doses to investigate effects, and neither reported the results of treatment over a long period. Campbell and Robertson[18] reported results similar to those of Restall and Smirk[9] in respect to relief of such manifestations as headache and breathlessness.

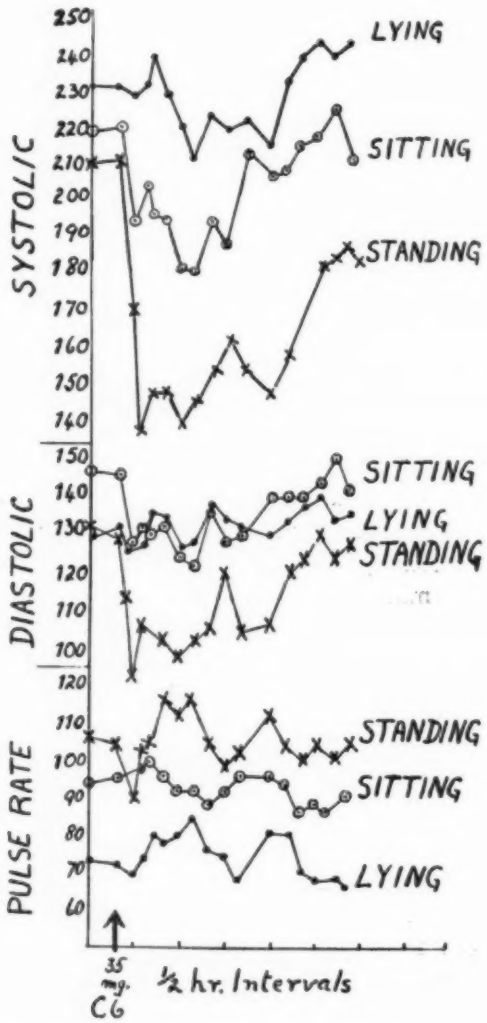

Fig. 1.—The effect of 35 mg. of hexamethonium bromide (C6) subcutaneously on the blood pressure in the lying, sitting, and standing postures in a patient with essential hypertension after sympathectomy. Corresponding results are obtained in most other forms of arterial hypertension.

In hospital patients confined to bed or a chair it seemed worth trying continuous, mechanically controlled subcutaneous injection in order to discover whether this would enable the blood pressure to be brought to a predetermined level for long enough to assist clinical investigation or possibly to treat the more severe cases.

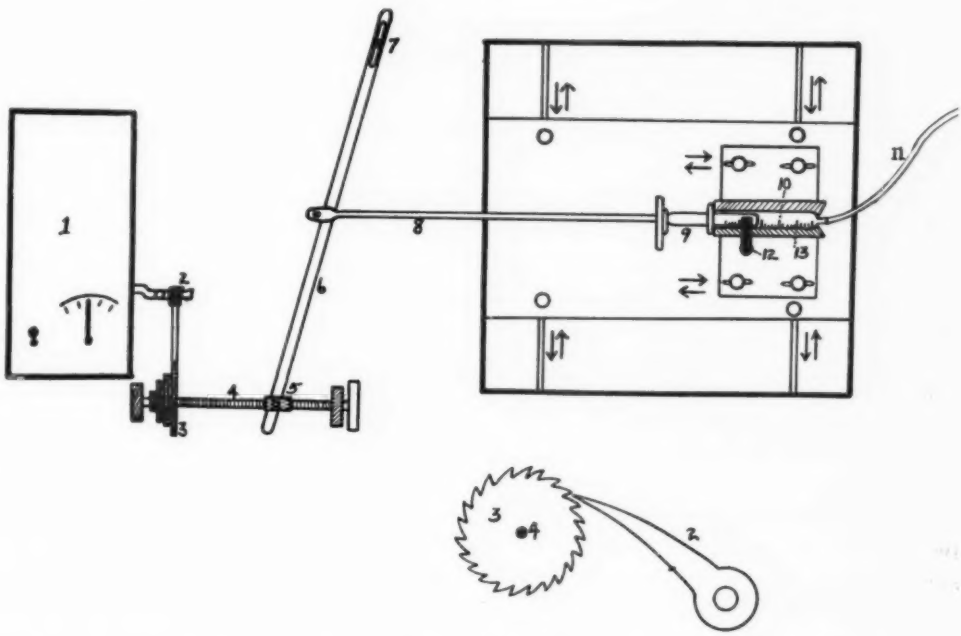

Fig. 2.—Apparatus for continuous injection of 1 to 100 c.c. over a period of two to thirty-two hours.

DETAIL OF THE ELECTRICALLY DRIVEN SYRINGE

The device (Fig. 2) empties most commercial syringes of capacity 1 to 100 c.c. and delivers whatever dose is placed in the syringe to the patient over the selected period of time as follows:

A variable speed, governor-controlled motor (*1*) operates an eccentrically mounted pawl (*2*) which rotates one of four cogged wheels (*3*) mounted to a common shaft (*4*). The speed of rotation of the shaft depends therefore on the cog selected. The shaft has a screw thread, and as the thread rotates it moves a nut (*5*) along its length. The nut is hinged to one end of a metal lever (*6*), the fulcrum (*7*) of the lever being at the other end. The moving end of the lever travels the length of rotating thread (10 cm.) in times which can be varied from two to thirty-two hours by appropriate adjustment of the motor speed and selection of the cogged wheel on which the pawl is to act. Hence, the movement of the lever which takes place at its attachment to the threaded shaft is 10 cm. and is zero at the fulcrum. Therefore, by bringing a suitably mounted rod (*8*) into contact with the appropriate point on the lever, the rod can be caused to make an excursion through a selected distance (between 10 and 0 cm.) in the desired time (between two and thirty-two hours.)

The rod is mounted so that it slowly thrusts home the plunger (*9*) of the syringe, and the barrel (*10*) is so placed that the end of the thrust of the plunger corresponds to the just empty position of the syringe. The contents of the syringe are conveyed to the injection needle by fine pressure tubing (*11*).

A simple device at the fulcrum (*7*) alters the effective length of the lever during movement so that the movement of the piston is always proportional to the rate of rotation of the threaded shaft. The syringe barrel (*10*) is held (*12*) in one of a series of V blocks (*13*) adapted so that the instrument will carry any syringe from 1 to 100 c.c. caliber. Once the syringe is in position, there are locking devices (not shown) which make it impossible for the barrel to shift its position or for the plunger to be moved inadvertently. The machine is switched off automatically (not shown) at the end of the stroke by a simple device operated by the lever.

EFFECT OF CONTINUOUS INJECTION OF METHONIUM HALIDES

With rates of continuous injection suited by trial to the individual and with the patient propped up in a cardiac bed, the blood pressure in patients with severe hypertension of various kinds has been maintained for eight hours to ten days at much reduced or sometimes approximately normal levels (Fig. 3) and with few side effects beyond dryness of the mouth. In a few instances side effects, which are referred to later, are more prominent, but in no case were they severe or difficult to alleviate. In most instances they were dispersed by prompt lowering of the head of the bed. The benefits of propping up the patient are that advantage is taken of the postural fall of blood pressure and that, if the pressure is falling too low, it can be restored in a few minutes by returning the patient to the horizontal position or, if necessary, by raising the foot of the bed on blocks. With a technician who had an understanding of the effects of posture following the course of the blood pressure, we have had no anxieties. Until the effect of a given rate of injection is known, the patient should not be left unattended, as the patient may be comfortable when the blood pressure level is only just above the threshold for symptoms. For patients with pressures over 200/120 mm. Hg the symptom level has been found as high as 170/110 mm. Hg and as low as 95/78 mm. Hg. As the patient becomes habituated to a lower blood pressure, the level at which symptoms appear falls, or symptoms do not appear unless the blood pressure is below normal.

If the injection is given from the start at a constant rate, then a rate of administration suitable for continued symptomless injection will take two to four hours to reach the desired low level of blood pressure. For this reason, when starting the injection it may be better to administer separately an appropriate initial dose (15 to 200 mg., according to the degree of tolerance to the drug) to approximate the blood pressure to the desired level and then to maintain a stable level by the rate of injection which preliminary trials have indicated (100 to 1,000 mg. per twenty-four hours). Early in the course of injection there is a rapid increase in tolerance to the drug, and the total amount of pentamethonium or hexamethonium given daily may have to be increased fivefold. Hence, the rate of injection will need frequent increase in the early stages of treatment.

This method of administration is associated in some patients with a number of minor complaints, such as temporary difficulty in emptying the bladder, flatulence, dryness of the mouth, decrease of appetite, and occasionally vomiting, but many patients are symptomless and few distressed. Faintness may occur if the blood pressure falls excessively. Frequently, after a few trials it is possible to reduce the blood pressure of hypertensive patients to a normal or close to normal

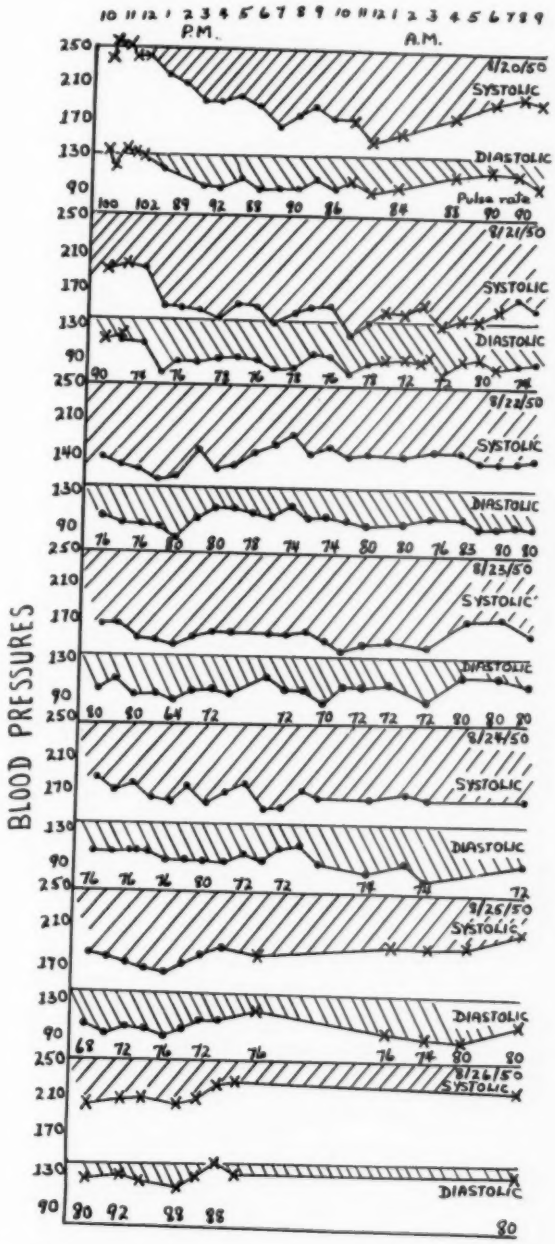

Fig. 3.—Effect of continued subcutaneous injection of hexamethonium bromide (C6) on the blood pressure and pulse rate in malignant hypertension.

Line with circles = administration in progress.

Line with crosses = administration not in progress.

The graph is subdivided into seven sections representing blood pressure changes through seven successive days. After administration ceased, the blood pressure took over twenty-four hours to return to normal.

The shaded areas represent the degrees of fall in the systolic and diastolic pressures. The figures inscribed below the graphs are the pulse rates.

level. Our initial experience in eleven patients is restricted to periods of up to ten days, but it is clearly possible to maintain substantial blood pressure reductions for many hours or days without causing symptoms which seem important to the patient. Where control of the blood pressure level for many hours or days would be valuable, the method of continuous subcutaneous or intravenous injection may help.

SUMMARY

1. Two or three subcutaneous injections daily of pentamethonium or hexamethonium halides offer a satisfactory method of reducing high blood pressures, provided that advantage is taken of the greater falls of pressure which occur in the sitting or standing posture with these autonomic ganglion blocking agents.

2. Initial results show that great clinical improvement commonly follows effective control over the blood pressure level by these drugs.

3. Continuous injection of methonium halides has been effected by an electrically operated syringe emptying device, made to carry syringes of 1 to 100 c.c. and to empty a syringe at a uniform rate in times ranging from two to thirty-two hours. Fine pressure tubing conveys the drug solution from the syringe to the injection needle. The slowest injection rate is 1/32 c.c. and the fastest 50 c.c. per hour. The intermediate rates are obtained by gears and regulation of the driving speed by a governor.

4. With continuous subcutaneous injection of methonium halides the blood pressure has been held within a selected range for periods up to ten days. The method appears to offer a greater control over the level of the blood pressure than has hitherto seemed practicable and has been of outstanding value in the treatment of hypertensive crises.

Thanks are due to Dr. G. L. Glasgow and to Dr. J. R. Presland for their assistance and to the Medical Research Council of New Zealand which defrayed the expenses of this work.

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REDUCTION OF MORTALITY RATE IN CORONARY ATHEROSCLEROSIS BY A LOW CHOLESTEROL-LOW FAT DIET

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A HIGH cholesterol-high fat diet has been stated by numerous observers to be directly implicated in the development of atherosclerosis.[4,8,10,20] Up to the present time, however, specific evidence for this concept has been supported only by high cholesterol-high fat feedings in experimental animals, such as those determined by Anitschkow,[1] Steiner,[2] Morrison,[3] and others.[4-6]

In this communication the author presents evidence in human subjects that the high cholesterol-high fat diet may be an important contributory factor to the production of atherosclerosis. Due to the well-known difficulty[7] in clinically diagnosing atherosclerosis and arteriosclerosis, the author studied the effects of diet in patients with recent proved coronary thrombosis and myocardial infarction. Since these patients have been shown to have coronary atherosclerosis in approximately 90 per cent of all cases, as pointed out by Gofman and associates,[8] Steiner,[9] and Morrison,[7] they were selected as being the most reliable and most representative of proved atherosclerotic subjects. In addition, these patients with coronary atherosclerosis present the clinician with a clinical problem of utmost seriousness and increasing frequency.

It has been pointed out by various investigators[7,9,10] that the term atherosclerosis is preferable to the old term arteriosclerosis since atheromatous disease of the arterial intima is responsible for the majority of clinical signs and symptoms as represented by coronary thrombosis, cerebral thrombosis, and peripheral vascular arteriosclerosis. Calcinosis of the medial coat of the artery, or Mönckeberg's arteriosclerosis, is deemed to be of minor or no clinical significance.[9] The term atherosclerosis is also more descriptive of the arterial disease due to the implication of the disorder in lipid or fat metabolism, and henceforth only the term atherosclerosis will be employed in this paper.

In examining the concept of the high-fat diet as the cause for atherosclerosis, it is noted that it is based on two sets of observations. (1) Comparative studies of autopsy material of various nationalities by Snapper,[11] Steiner,[12] Dock,[20] Hueper,[13] and others have demonstrated that in man a high-fat dietary intake seemed to be directly related to an increased incidence of atherosclerosis.[29] (2)

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The feedings of excessive amounts of cholesterol and fat in the rabbit,[1-6] the dog,[14,15] and the chick[16,17] have uniformly produced atherosclerosis comparable to that of the human subject.

The author felt that a desirable approach to this dietary question in atherosclerosis was a study of a series of fifty patients with proved coronary atherosclerosis over a period of three years on a low cholesterol-low fat diet. This series was compared to a comparable alternate series of fifty patients with proved coronary atherosclerosis who were on the "normal" or the average American dietary intake of cholesterol and fat for three years. Therefore, a total of 100 consecutive patients with recent proved coronary thrombosis and myocardial infarction was observed for a three-year period. Eighty-six men and fourteen women, whose ages ranged from 32 to 70 years, were studied. No patients were taken whose systolic pressures exceeded 180 mm. Hg. or whose diastolic pressures exceeded 110 mm. Hg. These patients presented (1) a characteristic clinical history of coronary thrombosis with myocardial infarction together with (2) typical and unequivocal electrocardiographic evidence of the same. Each patient had been hospitalized for the usual four to six weeks for the coronary thrombosis with myocardial infarction within a six-month period prior to the beginning of this study. The patients who had survived the initial infarction were taken in alternate order, one patient being placed on the low cholesterol-low fat diet and the next alternate patient on the usual prethrombosis diet. In this way fifty consecutive patients (8 female, 42 male) with an average age of 60 years were placed on a 20 to 25 Gm. fat daily intake for three years as shown in the accompanying charts. Fifty consecutive control patients (43 male, 7 female) with an average age of 62 years adhered to the customary cholesterol-fat intake which was judged to range from 80 to 160 Gm. of fat daily. As shown in the dietary table, the cholesterol content of the 20 to 25 Gm. daily fat intake is 50 to 70 mg. In the control series where the daily fat intake ranged from 80 to 160 Gm. of fat, the daily cholesterol intake ranged from approximately 200 to 1,800 mg. The fifty patients on the low-fat diet were given a diet whose caloric intake was placed at a maximum of 1,500 calories with an intake of approximately 320 Gm. of carbohydrate and 90 Gm. of protein. Other patients with hypercholesterolemia were encouraged to curtail further the daily fat intake to 8 Gm., the cholesterol intake to 10 to 20 mg., and the daily caloric intake to 1,200 calories in a suboptimal dietary range. On the diet prescribed, the vitamin A content was 9,753 I.U., 2.48 mg. of thiamine, 2.48 mg. of riboflavin, and 140 mg. of ascorbic acid, all of which are within normal requirements. A total vitamin oral supplementary capsule was taken in addition which more than doubled the daily vitamin intake. The mineral content of the diet was also normal, being approximately 1.009 Gm. of calcium, 1.792 Gm. of phosphorus, and 0.0222 Gm. of iron.

The mean weight at the outset for the forty-two men in the fifty dietetically treated patients was 166 pounds and 141 pounds for the eight women. Following the three-year low-fat diet, the mean weight for men was reduced to 145 pounds and 124 pounds for the women. The weights of the control series at the beginning and ending of the three-year period were not significantly altered.

The medication given equally in both these series of patients consisted of digitalis, aminophylline, nitroglycerin, or sedatives as required by any signs or symptoms of cardiac congestive failure and so forth in both series.

TABLE I. SURVIVAL RATES IN PATIENTS WITH CORONARY THROMBOSIS AND INFARCTION AFTER THREE YEARS

25 GM. FAT-CHOLESTEROL INTAKE			NORMAL PRETHROMBOSIS DIET		
NO. CASES	DEATHS	MORTALITY (%)	NO. CASES	DEATHS	MORTALITY (%)
50	7	14	50	15	30

TABLE II. ANALYSIS OF DEATHS IN FIFTY CORONARY THROMBOSIS PATIENTS TREATED BY LOW FAT-CHOLESTEROL DIET FOR THREE YEARS

CAUSE OF DEATH	NO. DEATHS	MORTALITY RATE (%)
Recurrent coronary thrombosis	3	6
Cardiac congestive failure	3	6
Extracardiac deaths	1	2

TABLE III. ANALYSIS OF DEATHS IN FIFTY CORONARY THROMBOSIS PATIENTS WHO CONTINUED ON PRETHROMBOSIS DIET

CAUSE OF DEATH	NO. DEATHS	MORTALITY RATE (%)
Recurrent coronary thrombosis	7	14
Cardiac congestive failure	6	12
Extracardiac deaths	2	4

Of the fifty patients on the low fat-low cholesterol diet it is seen from Table I that forty-three patients were living at the end of the three-year period of observation, or there was a mortality rate of 14 per cent. Of the fifty patients on their "normal" or prethrombosis diet, thirty-five were living after three years, or there was a mortality rate of 30 per cent. Table II gives a further breakdown of cause of death after the three-year period of observation. It is seen that of the dietetically treated patients, three died of recurrent coronary thrombosis with myocardial infarction, three of cardiac congestive failure, and one of pneumonia. In the nondietetically treated patients (Table III), seven died of recurrent coronary thrombosis and infarction, six of cardiac congestive failure, and two of acute cerebrovascular accidents.

Serum lipid and lipoprotein studies were made in these patients and are the subject of a separate communication. It may here be said, however, that considerable reductions in all fractions of the serum lipids occurred in most cases after the three-year period of dietetic treatment. The mean drop for total serum lipid levels was from 840 mg. before treatment to 571 mg. after three years of treatment. The mean drop of neutral fat fatty acids was from 236 mg. before treatment to 120 mg. after three years of treatment; phospholipids fell from 292 mg. to 231 mg. and the serum cholesterol level from 312 mg. to 220 mg. The rapidity of the drop in serum levels was in the order noted above, i.e., the total lipids were most rapid and the serum cholesterol levels least so. It was found that an appreciable number of patients required from one to two years on the low-fat dietary regime before a fall in serum cholesterol was manifested. A minority of patients showed no tendency to significant fall in serum cholesterol levels. This was particularly true in the early phases (under one to two years) of observation.[2] These may have been cases of heredofamilial cholesterolemia, described by Adlersberg and associates[19] and Wilkinson and associates.[18] The fall in serum cholesterol levels on the low-fat diet is comparable to that reported by Kempner[21] on the rice-fruit diet for hypertension. A separate communication by the author[28] describes serum lipid fractions which were reduced to lower levels than those achieved by diet alone when a combined low fat-low cholesterol diet was employed together with other therapeutic measures.[21]

It is possible that more effective reductions in both weight and serum lipid fractions may have been effected had the patients been on a rigidly controlled low cholesterol-fat diet as pointed out by Wollaeger and co-workers,[25] Keys and associates,[26] and Melinkoff and associates.[27] It is also possible that some patients may have either consciously or unconsciously taken a greater dietary fat intake than was prescribed; this could obviously affect mortality rates and serum lipid levels. However, it was not practical to effect rigid dietary control in these patients such as other observers have done by feeding their patients on a low fat-low cholesterol diet in a specially devised food commissary at a university.[22]

It was found that many of the patients who experienced angina pectoris on exertion, either before or immediately after recovery from their acute coronary thrombosis, noted that on the low-fat diet a reduction in severity of anginal pain occurred first and subsequently a reduction in frequency of attacks, despite the same amount of physical activity. It is also possible that this improvement was due in part to weight reduction and/or psychotherapeutic factors. Several patients with angina noted practically a complete disappearance of pain on exertion after the low-fat diet had been adhered to for periods varying between six months and 3 years. No clinical evidence of avitaminosis or other nutritional imbalance could be detected in this series of patients at the expiration of three years.

Additional factors which may have been responsible for the reduction in mortality rate in the dietetically treated patients are alterations in the coagulation time of the blood or alterations in circulation time resulting from loss of weight. The former possibility was ruled out by a "profile" of liver function

tests, including bromsulfalein, thymol turbidity, cephalin flocculation, albumin-globulin ratio, prothrombin time, circulation time, and coagulation and bleeding times. These were conducted at the outset and at the completion of the three-year period of time in the first fifteen patients; as they were within normal limits both before and after dietetic treatment, it did not appear to be indicated to do additional studies in the remainder of the patients. The only exceptions were several "positive" thymol turbidity and cephalin flocculation tests, both before and after treatment, as may be found in apparently normal individuals. Although the mortality rate in the dietetically treated patients was over 50 per cent less than the control group, it was realized that statistical evaluation was desirable. However, in reviewing the data of the paper, statisticians felt that they were not amenable to analysis by the chi^2, the Fischer t curve, or other statistical approaches. Although statistical analysis by a variant of the chi^2 method revealed a p value of 0.05, which may be regarded as probably a significant figure, no comparable series of samples on the controls and dietetically treated cases were available for statistical bases.

However, in the past two years the author and co-workers had placed an additional group of patients on a lower fat intake than herein described, i.e., an 8 Gm. daily fat intake which aimed at a more complete avoidance of any fat-containing food in the diet. To date, this series of patients has indicated an even lower mortality rate than reported in this paper and has made the author feel warranted in presenting these currently completed observations so that they may stimulate further controlled studies in a larger series of patients by other observers.

It should be noted that the author does not mean to interpret the reduction in morbidity and mortality rates in the dietetically treated patients as due to an arrest of the pathological process in the coronary arteries, although this may be one of the possible factors.

It was of considerable clinical interest to hear or note from many of the dietetically treated patients the following subjective symptomatic improvements: (1) increase in well-being, (2) increase in capacity for work, and (3) increase in morale or optimism. As noted previously, this may also be due in part to the factors of weight reduction and psychotherapy.

SUMMARY

1. One hundred patients with recent recovery from proved coronary thrombosis and myocardial infarction were studied over a three-year period as to the effect of a low cholesterol-low fat diet on the mortality and morbidity rates.

2. Fifty consecutive patients were placed on a daily 20 to 25 Gm. fat diet, and fifty alternate control patients were observed on the "normal" prethrombosis diet.

3. It was found that there was a trend toward a reduction in mortality and morbidity rates in coronary atherosclerotic patients on a 20 to 25 Gm. daily cholesterol-fat diet.

4. These studies suggest that a low cholesterol-low fat diet merits further controlled studies for the treatment of coronary atherosclerosis.

Grateful acknowledgement is made to Dr. W. F. Gonzalez, Dr. H. Sobel, and Dr. L. W. Smith and to E. Wolfson, M. Zwierlein, and P. Berlin for their aid in this study.

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LOW CHOLESTEROL-LOW FAT DIET*

Dietary Program

1. Avoid all foods high in cholesterol, such as all animal fats.
2. Do not use vegetable fats. (Plant sterols known as phytosterol and sitosterol are not absorbed by the gastrointestinal tract to any appreciable extent, but a high-fat diet seems to cause a larger synthesis of cholesterol.)
3. Adequate protein, 86 Gm. daily intake.
4. Carbohydrate, 230 Gm. daily.
5. Fat content, 20 to 25 Gm. daily: daily cholesterol content, 50 to 70 mg.
6. The use of a daily, supplementary vitamin preparation containing vitamin A concentrate is recommended.

Foods Permitted

Soups: Bouillon, fat-free vegetable soups, vegetable broths, and soups made with skimmed milk.
Meat, fish, and poultry: Lean meats, broiled, roasted, baked, or boiled.
Eggs: Egg whites as desired.
Milk and milk products: One pint or more of skimmed milk or buttermilk.
Vegetables: All cooked or raw, especially the green and yellow vegetables rich in vitamin A, namely, beet greens, chard, spinach, carrots, kale, and mustard greens.
Fruits: All fruits, raw, cooked, dried, and canned. Use citrus or tomatoes daily.
Salads: Any raw or cooked fruit or vegetable salad and gelatin salads. Serve with boiled or low-fat dressings such as those containing mineral oil (refined), lemon juice, spices, vinegar, ketchup, and so forth.
Cereals: All cooked or dry cereals. Macaroni, spaghetti, and rice. Serve with skimmed milk.
Breads: Whole-wheat, enriched white, or rye bread or rolls; graham and soda crackers.
Desserts: Fruit, tapioca, cornstarch, rice, sago, junket puddings made with skimmed milk and without egg yolks. Fruit whips made with egg whites, gelatin desserts, angel food cake, macaroons, and egg kisses, and water ices.
Beverages: Tea, coffee, or coffee substitutes; tomato juice, fruit or vegetable juices.

Foods to Be Avoided

Soups: Cream soups.
Meats: All glandular organs, as liver, brains, kidney, and sweetbreads. Pork and very fat meats, fat fish, and fish roe.
Milk and milk products: Whole milk, cream, Cheddar, Swiss, and all rich cheese and cheese spreads; excessive butter and butter substitutes.

***Although this dietary program was employed for this series of fifty patients, the author now prescribes an 8 Gm. fat daily intake in which the three daily allowances of vegetable oleomargarine (15 Gm.) are omitted from the diet in patients with appreciable hypercholesterolemia or familiohereditary hypercholesterolemia.**

Eggs: Egg yolks.
Breads: Hot breads, pancakes, waffles, coffeecakes, muffins, doughnuts, Ritz crackers.
Desserts: Any made with cream and egg yolks. Pies, frozen creams, rich cakes, and cookies.
Concentrated fats: The use of fats in any form, as salad dressings, olive or vegetable oils, suet, chicken or pork fat.
Miscellaneous: Rich gravies, olives, nuts, and avocados.

MEAL PLAN	SAMPLE MENU	AMOUNT	
		GRAMS	MEASURE
Breakfast			
Fruit juice	Orange juice	200	6 2/3 ounces
Cereal	Shredded wheat	30	1 biscuit
Skimmed milk	Skimmed milk	120	8 ounces
Bread	Whole-wheat toast	40	2 slices
Butter substitute	Vitamin-enriched vegetable margarine*	5	½ square
Sugar	Sugar	15	3 teaspoons
Hot beverage	Coffee, tea, postum		
Noon Meal			
Soup	Skimmed milk pea soup	150	5 ounces
Meat	Cold roast lamb, lean	60	2 ounces
Vegetables	String beans	100	¾ cup
Salad	Sliced tomato	100	1 medium
Fruit or dessert	Canned pineapple	100	1 slice
Bread	Whole-wheat bread	40	1 slice
Butter substitute	Vitamin-enriched vegetable margarine*	5	½ square
Milk	Skimmed milk	120	8 ounces
Evening Meal			
Fruit cocktail	Grapefruit cocktail	100	½ medium
Meat	Lean meats	60	2 ounces
Potato	Baked potato	150	1 medium
Vegetables	Asparagus	100	6-8 stalks
	Banana squash	100	½ cup
Salad	Fresh pear salad	100	1 medium
Salad dressing	Boiled dressing	20	1 tablespoon
Dessert	Lemon sherbert	90	1/8 quart
Bread	Whole-wheat bread	30	1 slice
Butter substitute	Vitamin-enriched vegetable margarine*	5	½ square
Milk	Skimmed milk	120	8 ounces

Special Instructions

Avoid oysters, caviar, or roe.

Serve only lean meat or fish.

Egg whites may be used as desired.

Allow 1 pint or more of skimmed or buttermilk daily.

Use only skimmed milk cheese such as cottage cheese. Omit rich cheese, such as cream or Cheddar.

Use no animal fats such as lard and suet in cooking.

Use vegetables and fruits as desired, prepared without extra butter and cream. (Plant sterols known as phytosterol are not absorbed by the gastrointestinal tract to any extent.)

Prepare tapioca, cornstarch, rice pudding and junket with skimmed milk and without egg yolk. Whips may be made with gelatin or egg whites, no cream.

The vegetables included in this diet are asparagus, broccoli, carrots, green beans, kale, yellow squash, pumpkin, spinach, turnip greens, and other greens; tomato (fresh, canned, or juice); vegetables commonly served as raw, as celery, cucumber, lettuce, and cabbage; and other cooked vegetables as beets, eggplant, onions, rutabagas, and cauliflower.

Approximate Composition of the Diet

Carbohydrate 230 Gm., protein 86 Gm., fat 23 Gm., calories 1,500
Calcium 1.054 Gm., phosphorus 1.628 Gm., iron 0.012 Gm.
Vitamin A 9,491 I.U., thiamine 1.87 mg., riboflavin 2.96 mg., ascorbic acid 127 mg.
Cholesterol content 70 mg.

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HEART DISEASE OF UNKNOWN ETIOLOGY

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IN THE past five years the authors have had the opportunity of observing nine cases of heart disease for which no etiological agent could be found. Similar cases have been described in the literature from time to time.[1-4] It is our purpose to present these additional cases in an attempt to add to the knowledge of heart disease of unknown etiology. Such cases have been previously classified into two large groups, namely, myocarditis of unknown etiology[6-11] and idiopathic hypertrophy of the heart.[2-5]

CASE REPORTS

CASE 1.—L. V., 35 years old, a Negro porter, was first admitted to the hospital on Oct. 22, 1945, complaining of shortness of breath, swelling of the ankles, and palpitation. During his last two years of Army service (1944 to 1945), the patient had had several widely spaced episodes of palpitation and lightheadedness. These episodes lasted only two to three minutes and occurred when he was tired or occasionally awakened him from sleep. Physical examinations at that time and upon discharge from the service were negative. He was in good health otherwise until one week before admission when he had night sweats and generalized aching of the joints, lasting forty-eight hours and followed in the intervening week by symptoms of congestive heart failure.

Physical examination revealed the patient to have dilated neck veins, râles in the lung fields, ascites, a liver palpable at the level of the umbilicus, and dependent edema. The heart was greatly enlarged to the left. A harsh, systolic murmur was audible over the entire precordium, but was loudest at the apex. Heart tones were distant. Blood pressure was 104/90 mm. Hg, and the pulse was feeble.

Laboratory studies were nonrevealing except for persisting microscopic pyuria. The serologic test for syphilis was negative, the hemogram was within normal limits, and one blood culture was negative. Chest roentgenograms demonstrated massive cardiac enlargement and congestion of the lung bases. An electrocardiogram showed inverted T waves in Lead I and flat T waves in Lead II. The patient improved on treatment. The clinical diagnosis was rheumatic valvular heart disease.

On Sept. 8, 1949, the patient was readmitted to the hospital because of congestive failure of one week's duration. During the preceding year he had felt well except for occasional palpitation despite discontinuance of digitalis and salt restriction. There was dullness to percussion at the

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This study was accomplished in conjunction with the Heart Clinic of the Indianapolis General Hospital from which some of this material was obtained.

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lung bases, and the liver was felt 3 fingerbreadths below the costal margin. Results of examination of the heart were the same except for a hyperactive precordium and a questionable friction rub at the apex. Cardiac fluoroscopy showed the heart to be enlarged and globular, and there was shifting of the heart silhouette on position change. These findings and the change in heart size on progress films were strongly suggestive of pericardial effusion; however, pulsations on fluoroscopy were good. The electrocardiogram suggested left ventricular hypertrophy. Questionable diastolic murmurs were heard at the apex on two occasions. The diagnosis on discharge was unchanged.

The patient was last admitted to the hospital on Dec. 19, 1949, with symptoms of "right heart failure." In the preceding months pulsus paradoxus had been noted by his physician. There was considerable increase in the heart size on the roentgenogram as compared to roentgenograms taken in November, 1948 (Fig. 1). Response to treatment was poor, and signs of failure increased. Engorgement of veins of the forehead and shoulders was noted when the patient

Fig. 1 (Case 1).—Roentgenogram of chest showing generalized cardiac enlargement.

was recumbent, the blood pressure levels fell to 96/80 mm. Hg, and the venous pressures were exaggerated on hepatic pressure. Roentgenkymography revealed diminished pulsations at the left cardiophrenic angle. Angiocardiography was not satisfactory, but a "suggestion" of dye was seen in the right auricle, apparently 2.5 cm. from the pericardial border. Pericardial aspiration failed to yield fluid. The patient died on May 16, 1950, during induction of anesthesia for pericardial resection (cyclopropane ether and oxygen). The diagnosis, clinically, was constrictive pericarditis.

Autopsy.—The findings of interest were limited to the heart and viscera. Two hundred cubic centimeters of frank blood were present in the pericardial cavity, but the pericardial surfaces were smooth and glistening. The heart was enlarged, dilated, and weighed 650 grams. Both auricles and ventricles were hypertrophied and dilated. The valves and coronary vessels were normal. Sections cut through the myocardium revealed no evidence of degeneration or fibrosis. Microscopic study demonstrated hypertrophy of the muscle bundles with enlarged nuclei, some of which

were hematoxophilic. One section showed an area of swelling of muscle bundles with disintegrated fibers. No Aschoff bodies were seen. Occasional small groups of lymphocytes were seen about a few arterioles, and there was a slight amount of patchy lymphocytic infiltration in the subepicardium of the auricles. The lungs, liver, and spleen demonstrated chronic passive congestion. The kidneys were grossly and microscopically negative.

Comment.—The hemopericardium is believed to be the result of attempted pericardial aspiration.

CASE 2.—H. R., 34 years old, a Negro laborer, was admitted to the hospital on Oct. 17, 1946, complaining of shortness of breath and swelling of the legs. The past history was not contributory. The patient had been in perfect health until one month prior to admission when he first noted increasing shortness of breath. This was followed by cough and expectoration and finally by swelling of the ankles.

Physical examination revealed a well-developed, adult, Negro man who was orthopneic. There was moderate distention of the veins of the neck. The blood pressure was 102/92 mm. Hg, the pulse was 100, and the respirations were 22. There were fine crepitant râles at both bases. The point of maximal impulse was seen in the anterior axillary line 13 cm. from the mid-sternal line. The rhythm was regular. There was a systolic murmur at the apex. P_2 was louder than A_2. The liver was palpable 2 fingerbreadths below the costal margin, and there was moderate edema of the ankles.

Laboratory studies on admission revealed three negative blood cultures. Urinalysis was negative.

A roentgenogram of the chest on Oct. 18, 1946, revealed marked cardiac enlargement, and on Nov. 13, 1946, another chest film revealed a pulmonary infarct in the right lung base. By Nov. 21, 1946, there was considerable decrease in the size of the heart. The electrocardiogram revealed low-voltage T waves in Leads I, II, and III and broad P waves in Leads I and II.

On routine cardiac management the patient improved, but on Nov. 8, 1946, he complained of pain in the right chest with hemoptysis. He continued to expectorate blood until Nov. 15, 1946; then he gradually improved and was discharged on Nov. 27, 1946. The clinical diagnosis was rheumatic valvular heart disease.

He was readmitted to the hospital on Aug. 16, 1947, because of an upper respiratory infection. He had worked until two days prior to admission and had done very well. Physical examination revealed the blood pressure to be 108/94 mm. Hg. X-ray examination again revealed marked enlargement of the heart. There was no change in the electrocardiogram.The patient was admitted for the third time in September, 1947, for shortness of breath and swelling of the ankles. He improved and returned to work. The last admission was on Aug. 1, 1950. He stated that during the interval from December, 1947, up to the final admission he had done poorly and had been unable to work because of shortness of breath. He was treated by his local physician with mercurial diuretics twice a week and had continued a low-sodium regime and digitalis. During the latter part of July, 1950, shortness of breath increased and his private doctor advised hospitalization. Physical examination revealed an acutely and chronically ill, adult man who was dyspneic and orthopneic. The blood pressure was 140/80 mm. Hg. The apical rate was 76 and the radial rate 44. There were fine râles at both lung bases. Examination of the heart revealed frequent premature contractions and a systolic murmur at the apex. The liver was palpable 3 fingerbreadths below the costal margin, and there was 3 plus edema of the ankles. On the day following admission, the patient suddenly died while sitting up in bed.

Autopsy.—The pertinent findings were limited to the heart and lungs. The lungs revealed moderate pulmonary edema. There were old scars, consistent with healed pulmonary infarcts, in both lungs. The heart weighed 830 grams, and enlargement was predominately that of the right ventricle. The valves, coronary arteries, and pericardium were all grossly normal. There was a moderate amount of diffuse subendocardial fibrosis. Microscopic study revealed minimal fibrosis of the myocardium. There were many large myocardial nuclei with moderate hypertrophy of the muscle fibers (Fig. 2). Glycogen stain showed only a minimal amount of glycogen

distributed throughout the muscle fibers. There was an old infarction of the right kidney which was almost completely healed; otherwise, gross and microscopic studies of the kidneys were normal.

CASE 3.—W. von S., 48 years old, a white male carpenter, was admitted to the hospital on Jan. 13, 1948, complaining of shortness of breath and cough. For thirty years the patient had had a moderately heavy and steady alcohol intake. He stated he had been refused work on several occasions between 1940 and 1942 because of hypertension, and he had noted very mild dyspnea on exertion. However, at the time of Army induction, the physical examination had been normal,

Fig. 2 (Case 2).—Section of heart muscle demonstrating fibrosis, large, deeply stained nuclei indicative of hypertrophy, and slight cellular infiltration.

and blood pressure was recorded as 140/90 mm. Hg. In March, 1944, he was admitted to an Army hospital, complaining of fatigue and mild dyspnea on exertion, "such as a three or four-mile hike." During the preceding eighteen months, the patient stated he had recurrent, sharp, nonradiating precordial pains which usually came at night and awakened him and which at times were accompanied by a smothering feeling. The pain was not severe. Physical examination was negative. The blood pressure was 130/70 mm. Hg. Serum cholesterol was 300 mg. per cent, and the basal metabolism rate was −17. A roentgenogram of the chest was normal. The electrocardio-

gram demonstrated low voltage of the QRS complexes with flat to inverted T waves. There was no appreciable change in the electrocardiographic findings after several days of treatment with thyroid extract. The patient was discharged from the Army in May, 1944, because of undiagnosed heart disease. Since that time, and especially in the preceding two years, he had noted increasing fatigue, dyspnea on effort, and cough. Two weeks before admission, the symptoms increased, and the cough became productive.

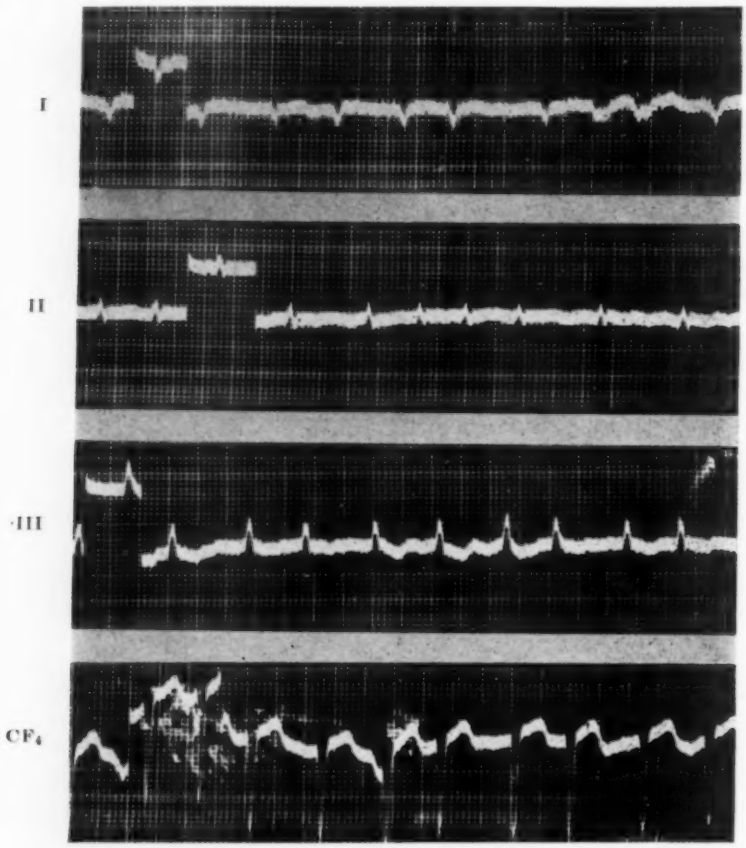


Fig. 3 (Case 3).—Electrocardiogram showing low voltage of the QRS complexes and auricular fibrillation with an average ventricular rate of 120.

Physical examination revealed a very dyspneic and cyanotic man with a temperature of 100° F. The scleras had an icteric tinge. The retinal vessels revealed an arteriovenous ratio of 1:3, but were otherwise normal. The neck veins were distended, moist râles were heard over the lung bases, and the liver was palpable 3 fingerbreadths below the costal margin. The blood pressure was 100/80 mm. Hg, and there was rapid auricular fibrillation with a marked pulse deficit. The heart was enlarged to the left, tones were faint, and no murmurs were heard.

A blood Kahn test was negative. The white blood count was 15,400 with a normal differential, and there was a mild hypochromic anemia. The urine contained a trace of albumin and frequent granular casts; specific gravity was 1.016. Serum bilirubin was 10 mg. per cent. Nonprotein nitrogen levels varied from 42 to 80 mg. per cent. Chest roentgenograms demonstrated cardiac enlargement and a small amount of fluid at the left base. Electrocardiograms revealed low voltage and flattened T waves. Rapid auricular fibrillation and occasional ventricular premature systoles were seen (Fig. 3).

Despite treatment, congestive failure increased. The heart rate was rapid, and blood pressures were low, with small pulse pressures. Roentgenkymography was not informative. A pericardial aspiration failed to yield fluid. The patient then developed gross hemoptyses and mild chest pains and died of cardiac failure. The clinical diagnosis was chronic myocarditis.

Autopsy.—The important findings were restricted to the heart and lungs. The pericardial sac contained a small amount of clear fluid, but the surfaces were normal. The heart was markedly dilated and weighed 530 grams. The myocardium, on cut section, was a dusky, pale, grayish-brown color, and ante-mortem thrombi were found in both auricular appendages. All valves and coronary vessels were normal. Microscopic study revealed varying degrees of fibrosis and hypertrophy. Some sections were almost normal, and in others there was extensive fine fibrosis separating muscle fibers and muscle bundles themselves. Cellular reaction was negligible, there being only slight associated infiltration with lymphocytes and reticuloendothelial cells. The muscle fibers were hypertrophied, and nuclei were large. No Aschoff bodies were seen. Necrosis and evidence of vascular disease were absent. Multiple pulmonary infarcts were found in all lobes of the lungs, and pulmonary edema was evident. The viscera demonstrated chronic passive congestion. Microscopic sections showed hemorrhagic infarction of lung. The liver revealed severe chronic passive congestion and some evidence of cardiac cirrhosis. The kidneys were normal grossly except for the presence of fetal lobulations; microscopic study revealed no abnormalities.

Comment.—Despite the history of occasionally elevated blood pressure recordings, it is not felt that hypertension played any significant part in the etiology of this man's heart disease. The patient's Army records were reviewed, and the findings of hypertensive disease were not recorded; subsequent physical findings, roentgenograms, and electrocardiograms do not lend credence to such a diagnosis, and, finally, the post-mortem examination failed to support hypertension as an etiological factor.

CASE 4.—W. H. S., 39 years old, a white male bartender, was admitted to the hospital on Nov. 30, 1948, complaining of shortness of breath and swelling of the feet of four months' duration. The patient had been well in the past except for a vague history of dyspnea and collapse occurring on one occasion between 1943 and 1945 while he was in the Army, but he had no pain at that time, and his service records did not record the incident. In 1943, when he was examined for hemorrhoids, the patient gave a history of "some shortness of breath for 10 to 12 years." The past history was otherwise nonrevealing, and the patient had felt well until the onset of the complaints of dyspnea on exertion, nonproductive cough, orthopnea, and nocturnal dyspnea. Three weeks before admission he noted pedal edema which had progressively extended to the level of the inguinal regions by the time of admission.

Physical examination revealed a dyspneic white man with a temperature of 98.6° F. Examination of the eye grounds was negative. There was venous engorgement of the neck veins, râles throughout the lungs, a palpably tender liver, a fluid wave in the abdomen, and generalized edema of the lower extremities and scrotum. Blood pressure was 95/55 mm. Hg, and the pulse was 88. The heart was enlarged slightly to the left. Heart tones were distant and no murmurs were heard.

Laboratory studies were negative. These included blood serologic tests for syphilis, a hemogram, urinalysis, kidney function tests, and serum protein determinations. The sedimentation rate was 38 mm. per hour. Chest roentgenograms and fluoroscopy showed cardiac enlargement, particularly of the left ventricle (Fig. 4). Electrocardiograms on three occasions revealed left bundle branch block.

Treatment for congestive failure resulted in improvement, and the clinical diagnosis on discharge was arteriosclerotic heart disease.

On Feb. 19, 1949, the patient was readmitted to the hospital with symptoms of congestive failure of one week's duration. Physical findings were similar to those of the previous admission, although at this time the patient was cyanotic. The pulse was 134 and irregular due to frequent

premature systoles. A diastolic gallop rhythm was noted on several occasions. Response to treatment was slower and less complete than on the first admission. The diagnosis on discharge was chronic idiopathic myocarditis.

The third and final admission for congestive failure was on June 23, 1949, symptoms having been present for two weeks. The patient was severely decompensated and moribund on admission. There was a mild hypochromic anemia. The white blood count was 19,300 with 89 per cent neutrophils and 11 per cent lymphocytes. Bedside chest roentgenograms demonstrated marked enlargement of the heart, pulmonary congestion, and increased density at the right lung base, believed due to pulmonary infarction. There was no change in the electrocardiogram. The patient grew worse rapidly. He had hemoptyses, vomited old blood, and passed tarry stools. Jaundice was observed, and the serum bilirubin rose to 7 mg. per cent. Death occurred fifteen days after admission.

Fig. 4 (Case 4).—Roentgenogram of chest demonstrates a moderately enlarged cardiac silhouette with minimal fluid in the right short fissure. An area of infiltration in the right base is consistent with a pulmonary infarct.

Autopsy.—The pertinent findings were restricted to the chest and abdomen. The parietal pericardium was adherent to the visceral pericardium over the right ventricle. Both layers were thickened. The heart was dilated and weighed 550 grams. Friable gray thrombi were present in all heart chambers. The muscle of the left ventricle was thickened, and an area of myocardial degeneration of lighter color and softer consistency was seen at its posterobasal portion. A few areas of very superficial subendocardial fibrosis were noted in both ventricles and the left auricle. The valves were normal except for the presence of an atheromatous plaque on the anterior leaflet of the mitral valve and several small, translucent, and rather firm excrescences along the free border of the leaflets of that valve. The proximal portion of the anterior descending branch of the left coronary artery was narrowed by a partially calcified plaque, but the remaining coronary vessels were normal. Microscopic study demonstrated hypertrophied muscle fibers with separation of muscle bundles. The nuclei of these fibers were prominent and exhibited square ends. No significant cellular or fibrotic changes were noted except for scattered areas of lymphocytes seen in the epicardium. In one section from the posterobasal left ventricle the muscle fibers were eosinophilic

and fragmented, and their nuclei did not stain well. Numerous polymorphonuclear cells, some red cells, and fibrin were present in the edge of this area of focal necrosis. No Aschoff bodies were seen. Partially liquified pulmonary infarcts were found in all lobes of the lungs, and these organs were edematous. The right pleural cavity was obliterated by adhesions, and many adhesions were found at the base of the lower left lobe between the lungs and diaphragm and between the pleura and pericardium. The liver and spleen also demonstrated chronic passive congestion. Adhesions were present between the undersurface of the liver and surrounding structures. The mucosa of the lower two-thirds of the esophagus was ulcerated, and the exposed muscle fibers were black in color. Examination of the kidneys was negative except for a small infarct of the left kidney and a larger and older infarct of the right kidney.

Comment.—The atheroma in the anterior descending branch of the left coronary artery is not felt to have been a significant factor in the etiology of this patient's heart disease. The small lesions on the mitral valve are believed to represent ante-mortem, nonbacterial, verrucous vegetations.

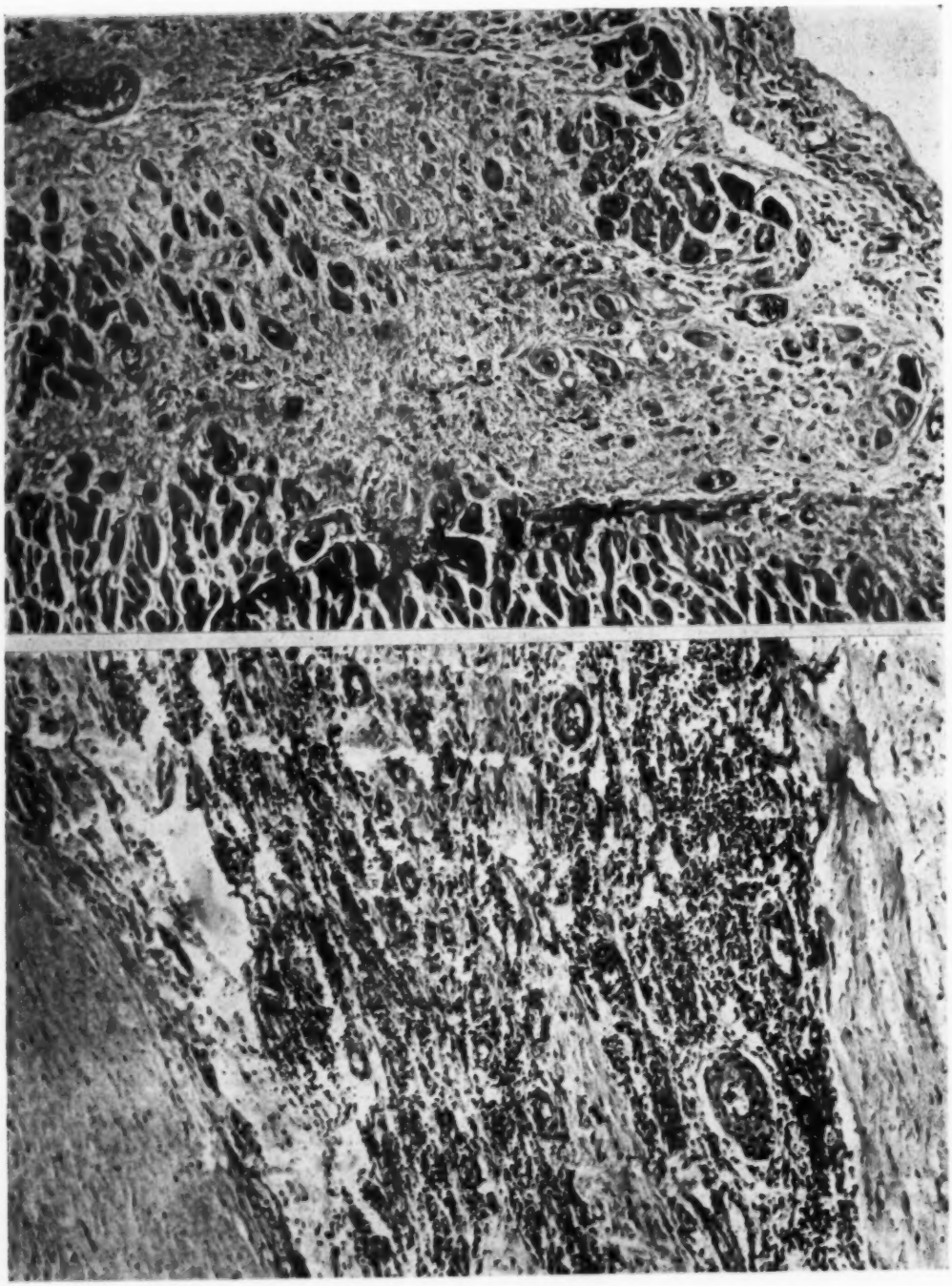
CASE 5.—T. W., 33 years old, a Negro laborer, was first admitted to the hospital on Dec. 16, 1948, complaining of shortness of breath, weakness, and swelling of the ankles. He had been well and working until October, 1948, when he was forced to stop because of shortness of breath, abdominal distention, and swelling of the ankles. Progression of these symptoms, along with a weight loss of 30 pounds, prompted admission to the hospital. The past medical history was negative, except for an excessive alcohol intake over a period of eight to ten years. The family history revealed that the mother and a brother died of "heart attacks" at the ages of 65 and 38 years, respectively.

The physical examination on the first admission revealed moderate dyspnea and cyanosis. The patient was afebrile. The pupils reacted sluggishly to light, and the eye grounds were negative. The lung fields were clear. The heart rate was 104 and the rhythm regular. The highest blood pressure during this admission was 130/115 mm. Hg. There was marked cardiac enlargement with embryocardia and a low-pitched, apical, systolic murmur. No pericardial friction rub was heard. The liver was enlarged and tender, and pedal edema was marked.

Except for positive blood and spinal fluid Wassermann tests and a trace of albumin in the urine, the laboratory findings on entry were negative. These included hemogram, sedimentation rate, and nonprotein nitrogen determinations. The chest roentgenogram on admission revealed marked generalized cardiac enlargement. An electrocardiogram on admission revealed left ventricular hypertrophy.

The course during the first admission was uneventful, and the blood pressure returned to 110/80 mm. Hg when the patient became compensated. Subsequent laboratory studies, including repeated urinalyses, a "liver profile," a urea clearance study, and an intravenous pyelogram, were within normal limits. The patient was discharged on Jan. 7, 1949, with a diagnosis of heart disease of unknown etiology.

Throughout 1949 and 1950, there were six readmissions for recurrent bouts of congestive heart failure. On Nov. 8, 1949, he developed hemoptysis, chest pain, and severe dyspnea along with clinical and x-ray findings consistent with a pulmonary infarct. Also, during periods of severe decompensation there were transient blood pressure elevations to levels of 160/120 mm. Hg, but these pressures always returned to normal when the patient became compensated. The final admission was on Oct. 4, 1950, when he was admitted because of severe hemoptysis, right-sided chest pain, and marked congestive heart failure. The blood pressure was 100/80 mm. Hg. The total leucocyte count was 13,000, and the sedimentation rate was 18 mm. per hour. The chest roentgenograms revealed a right pleural effusion and marked cardiac enlargement. A clinical diagnosis of idiopathic hypertrophy of the heart was made at this time. The electrocardiogram revealed sinus tachycardia with left ventricular hypertrophy and ventricular premature systoles. He failed to respond to therapy and died on Nov. 3, 1950, approximately two years from the onset of the symptoms.



B.

A.

Fig. 5 (Case 5).—*A*, Section of heart muscle showing marked cellular infiltration more pronounced about the small vessels and with a moderate degree of replacement fibrosis of muscle fibers. *B*, Section of heart muscle showing marked necrosis of fibers with a severe degree of fibrosis.

Autopsy.—The pertinent findings were limited to the heart and viscera. The heart chambers were all markedly dilated, and the heart weighed 600 grams. Predominant hypertrophy and dilatation were found in the left ventricle. The endocardium was not remarkable. There were small ante-mortem mural thrombi in the right and left ventricles near the apex. There were no abnormalities of the valves and coronary arteries. Microscopic examination revealed the muscle fibers to be hypertrophied. There were occasional small areas of muscle degeneration and necrosis with fibrous replacement throughout the myocardium. Sections through the septum at the apex revealed the myocardium to be almost entirely replaced by necrosis with surrounding marked cellular infiltration (Fig. 5, *A* and *B*). Fibrosis was especially marked in the subendocardial region. There were occasional areas of perivascular lymphocytic and polymorphonuclear leucocytic infiltration. No Aschoff bodies were observed. The kidneys were grossly and microscopically normal. The right lung revealed multiple infarcts. There was marked chronic passive congestion of the viscera.

Comment.—In regard to the elevated blood pressures found in this patient, it seems well established that during decompensation protracted elevation of both systolic and diastolic blood pressures may occur and may be maintained for weeks. After the heart improves, the blood pressure then returns to normal.[12]

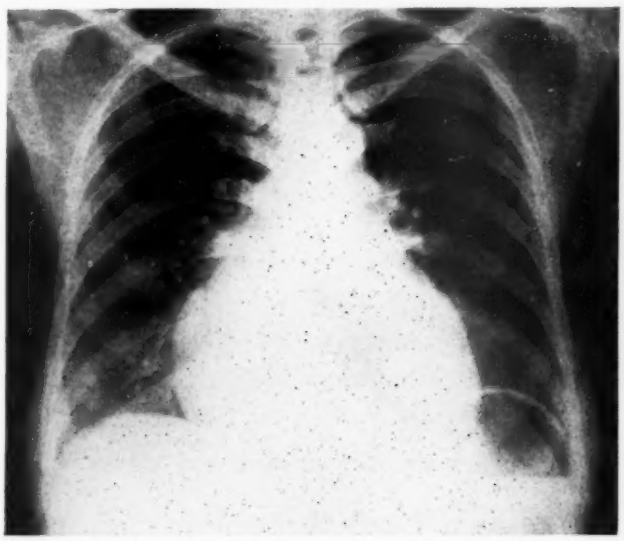


Fig. 6 (Case 6).—Roentgenogram of the chest demonstrating marked cardiac enlargement.

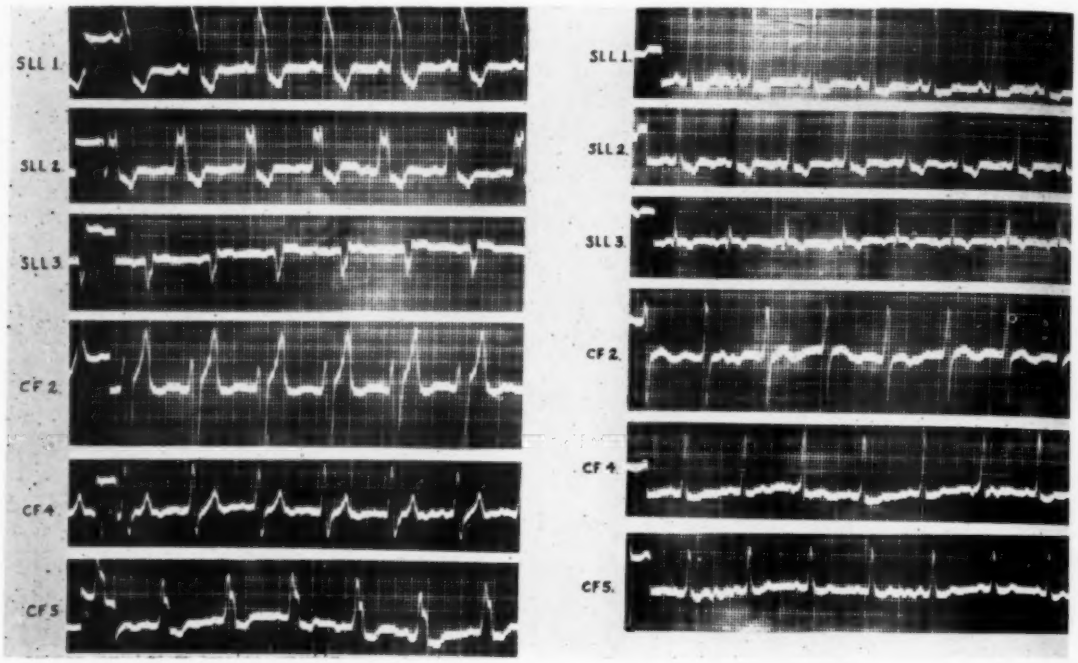
Case 6.—V. G., 24 years old, a Negro dayworker, was first admitted to the hospital on Dec. 20, 1948, complaining of "fluttering of the heart," shortness of breath, and swelling of the abdomen and feet. She had been in good health and was working in a convalescent home until this illness. On Dec. 13, 1948, she experienced a rather sudden onset of "fluttering of the heart" and subsequently developed increasingly severe shortness of breath and swelling of the abdomen and feet. The past medical and family histories were essentially negative except for a miscarriage in June, 1947.

The physical examination on the first admission revealed moderate dyspnea and slight cyanosis. She was afebrile. The eye grounds were negative. The lung fields were clear. The heart rate was 144, with a regular rhythm. The highest blood pressure during this admission was 120/80 mm. Hg. There was marked cardiac enlargement with good heart tones and a high-pitched, apical, systolic murmur. There was no pericardial friction rub. The liver was enlarged

Fig. 5 (Case 5).—*A*, Section of heart muscle showing marked cellular infiltration more pronounced about the small vessels and with a moderate degree of replacement fibrosis of muscle fibers. *B*, Section of heart muscle showing marked necrosis of fibers with a severe degree of fibrosis.

and tender, and there was marked pedal edema. The clinical impression was that of acute cardiac dilatation with congestive heart failure due to an unknown cause.

Except for a positive blood Wassermann test, the laboratory findings on admission were negative. These included urinalysis, hemogram, sedimentation rate, nonprotein nitrogen determination, serum protein values, and a sputum examination. Chest x-ray examination and cardiac fluoroscopy on admission revealed a globular cardiac shadow with symmetrical enlargement of both right and left ventricular chambers, along with diminished pulsations over all cardiac borders; the x-ray impression was that of a marked pericardial effusion (Fig. 6). The electrocardiogram on admission revealed a supraventricular tachycardia with aberrant conduction.



A. B.

Fig. 7 (Case 6).—*A*, Electrocardiogram demonstrating left bundle branch block. *B*, Electrocardiogram demonstrating the pattern of left ventricular hypertrophy. The undulations in Leads I and CF_4 are artifacts.

The course during the first admission was marked by the sudden onset of hemoptysis, tachycardia, fever, right-sided chest pain, and physical findings consistent with a pulmonary infarction on Dec. 25, 1948. At this time a chest roentgenogram revealed fluid in the right costophrenic sinus, the total leucocyte count rose to 12,000, and the sedimentation rate rose to 24 mm. per hour. Serial electrocardiograms revealed a transient change from a left bundle branch block to one of normal intraventricular conduction and left ventricular hypertrophy in March, 1949 (Fig. 7, *A* and *B*). Urea clearance studies during this period were normal. The patient experienced another bout of paroxysmal tachycardia on Feb. 14, 1949, and then gradually improved. She was discharged on June 24, 1949, with the diagnosis of heart disease of unknown etiology.

Except for occasional bouts of rapid heart action, the patient remained relatively asymptomatic until February, 1950, after which she again developed shortness of breath and experienced more numerous bouts of paroxysmal tachycardia. Examinations in the cardiac clinic revealed a marked increase in heart size clinically and fluoroscopically. There was an intermittent diastolic gallop, and the congestive findings became more pronounced. The final admission was on April 16, 1950, when she developed a sudden hemiplegia along with a marked increase in the congestive

phenomena. The blood pressure on this admission was 136/96 mm. Hg. The laboratory findings were within normal limits. She failed to improve and died thirteen days after admission.

Autopsy.—The pertinent findings were restricted to the heart, lungs, and brain. The heart chambers were all markedly dilated, and the heart weighed 610 grams. Predominant hypertrophy and dilatation were found in the left ventricle with lesser degrees in the right ventricle and both auricles. The endocardium was not thickened. There were ante-mortem mural thrombi adherent in the right auricular appendage and at the apex of the left ventricle. There were no abnormalities of the valves and coronary arteries. Microscopic examination revealed the muscle

Fig. 8 (Case 6).—Section of heart muscle showing marked fibrosis with moderate to marked cellular infiltration.

fibers to be hypertrophied. There was a rather large area of necrosis in the left ventricle near the septum and apex with a mural thrombus covering the endocardial surface over this area of necrosis. There was also considerable interstitial fibrosis with marked cellular infiltration of the myocardium (Fig. 8). No ante-mortem thrombi were seen in the smaller vessels and no Aschoff bodies were observed. The kidneys were grossly normal and microscopically revealed small infarcts. The lungs revealed multiple infarcts, including one in the right lower lobe. Findings in the other or-

gans were those of focal encephalomalacia of the left basal ganglia and chronic passive congestion of the viscera.

CASE 7.—J. T., 33 years old, a Negro clerk typist, was first admitted to the hospital on March 16, 1949, complaining of shortness of breath, pain in the right upper quadrant, and weakness. The patient had been perfectly well until three weeks prior to admission when he first noted shortness of breath upon exertion and a feeling of discomfort in the right upper abdomen. Dyspnea was marked even with slight exertion. The patient, however, continued to work until the day before admission when the symptoms became so severe that he called his private physician and hospitalization was advised. The past history was negative. There was a history of scarlet fever and mumps in childhood. Family history revealed that the father died at the age of 41 years of "acute indigestion."

Physical examination revealed a well-developed, adult, Negro man who was dyspneic and orthopneic. There was moderate distention of the veins of the neck in the upright position. The blood pressure was 95/70 mm. Hg. The pulse rate was 120. There were crepitant râles at both lung bases. There was a diastolic gallop rhythm at the apex. The heart sounds were distant, and there was a high-pitched systolic murmur at the apex. The liver was palpable 2 fingerbreadths below the costal margin.

Urinalysis revealed many pus cells per high-power field. The sedimentation rate was 10 mm. in one hour. A blood Kahn test was negative. Chest x-ray examination on March 16, 1949, showed marked enlargement of the cardiac shadow. There was obliteration of both costophrenic angles and a moderate amount of pulmonary congestion. An electrocardiogram revealed left bundle branch block.

Venous pressure in the antecubital vein was 240 mm. of water. The circulation time from arm to lung was prolonged. The patient improved on routine cardiac management and was discharged on April 11, 1949. The clinical impression was heart disease of unknown etiology.

The patient was readmitted on May 22, 1950, complaining of dyspnea and orthopnea. He stated that he had done well in the interim until three weeks prior to this admission when he again noted paroxysmal bouts of dyspnea, especially in the evenings and at bedtime. He went to his private physician who treated him with weekly injections of mercurial diuretics. However, the patient did not improve, and the doctor advised readmission to the hospital. Physical examination revealed a chronically ill Negro man, who was dyspneic and orthopneic. The blood pressure was 80/65 mm. Hg, the pulse rate 100. The point of maximal impulse was visible in the sixth intercostal space at the anterior axillary line. There were a systolic murmur and diastolic gallop rhythm at the apex. The liver was palpable 3 fingerbreadths below the costal margin. Laboratory studies, including hemogram, urinalysis, nonprotein nitrogen determinations, and serologic tests, were all within normal limits. Roentgenograms of the chest revealed marked enlargement of the cardiac silhouette. Fluoroscopic examination revealed the enlargement to be predominantly that of the left ventricule. The electrocardiogram was unchanged from the previous admission. The patient did not improve in spite of treatment, and on June 12, 1950, he complained of increasing dyspnea accompanied by pain in the right chest. The temperature rose gradually to 103° F., and he died seven days later. Permission for post-mortem examination was not granted.

CASE 8.—C. P., 44 years old, a Negro dayworker, was admitted to the hospital on Feb. 24, 1950, complaining of palpitation, shortness of breath, and swollen ankles. She had been in good health and was doing daywork until Feb. 17, 1950, when she suddenly developed shortness of breath, a nonproductive cough, and rapid heart action. Because of progression of these symptoms, along with swelling of the feet, she was hospitalized. The past medical history revealed that she had had a hysterectomy in 1940 for uterine fibroids and had had an uncomplicated pregnancy twenty years ago. The family history revealed that a grandfather died suddenly of a "heart attack," both grandmothers died of "heart trouble," and two cousins died suddenly of "heart attacks."

The physical examination on this admission revealed moderate dyspnea and cyanosis. She was afebrile. The eye grounds were negative. The lung fields revealed a few moist râles in both bases. The heart rate was 100, and the rhythm was regular. The highest blood pressure during this admission was 140/70 mm. Hg. There was marked cardiac enlargement with distant heart

tones, a soft apical, systolic murmur, and a diastolic gallop. No pericardial friction rub was heard. The liver was enlarged, and pedal edema was marked. The clinical impression was heart disease of unknown etiology.

Except for a persistently elevated sedimentation rate of 30 to 50 mm. in one hour, the laboratory findings were negative. These findings included urinalysis, hemogram, blood serologic test for syphilis, sputum examinations, and serum protein determinations. The chest x-ray examination and cardiac fluoroscopy revealed enlargement of both the right and left ventricles (Fig. 9). Serial electrocardiograms revealed a persistent complete left bundle branch block with ventricular premature systoles.

The course in the hospital was marked by gradual improvement, and the patient was released on May 16, 1950, with the same clinical impression. Since the release from the hospital, the patient has experienced intermittent bouts of palpitation followed by shortness of breath. The patient is still living.

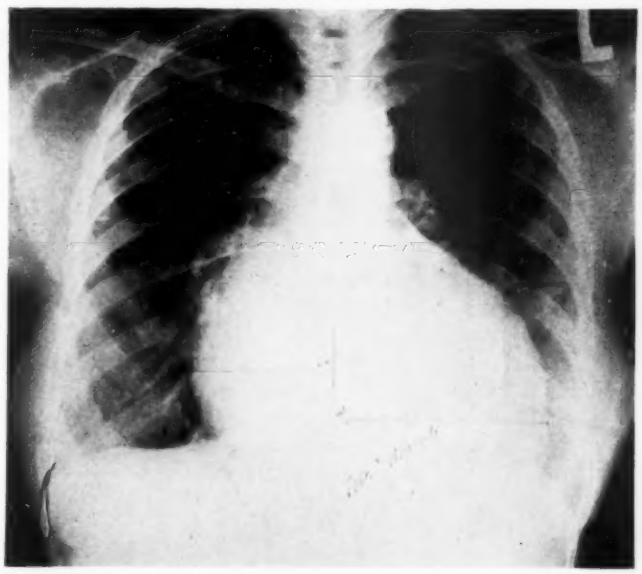


Fig. 9 (Case 8).—Roentgenogram of chest showing marked cardiac enlargement.

CASE 9.—J. F., 38 years old, a Negro dry cleaning plant worker, was first admitted to the hospital on Jan. 29, 1951, complaining of shortness of breath and swelling of the feet. Prior to this admission he had been in apparent good health until June, 1948, when he first experienced shortness of breath on exertion, but continued to work. In December, 1948, he first noted some swelling of the feet along with palpitation, weakness, and increasing dyspnea. He was admitted to Barnes Hospital, St. Louis, Mo., on May 19, 1948, with the chief complaint of dyspnea on exertion. The physical findings at that time revealed the patient to be afebrile. There were moist râles in the lung bases. The heart rate was 100. The blood pressure was 110/80 mm. Hg. There were marked cardiac enlargement with poor heart tones and a protodiastolic gallop at the apex. The liver was enlarged and tender. On May 26, 1949, he developed right flank pain, and the temperature rose to 39.6° C. It was felt that he probably had a right perinephritic abscess or an infected renal infarct. Except for a few red blood cells in the urine, the laboratory findings on entry were negative. He was discharged under protest on June 9, 1949, with the diagnosis of "enlargement of the heart due to unknown cause (?subendocardial fibrosis)."

Because of a recurrence of the above symptoms, he was admitted to Hubbard Hospital of Meharry Medical College, Nashville, Tenn., in December, 1949, when a diagnosis of right lobar pneumonia and left ventricular hypertrophy was made. The length of this hospitalization is unknown. He was again admitted to the Hubbard Hospital in May, 1950, because of a recurrence

of symptoms. On this admission the blood pressure was 110/60 mm. Hg. There was enlargement of the heart, both clinically and fluoroscopically. There were a suggestion of a presystolic rumble and a loud first heart sound at the apex. The liver was enlarged. There was no edema. The laboratory findings revealed a negative urinalysis, a sedimentation rate of 4 mm., and a positive blood Kahn test. The electrocardiogram revealed a low T_1, inverted T_2, elevated RS-T segments in $V_{2,4,5}$, a heart rate of 64, a P-R interval of 0.16 second, and a QRS of 0.08 second. He was discharged with a diagnosis of "heart disease of unknown cause."

The patient remained asymptomatic and was working in a dry cleaning establishment until about six weeks prior to this admission when he exhausted his supply of medicine and gradually developed increasing shortness of breath and swelling of the feet to the point of frank congestive heart failure. The past medical history revealed that he was treated for syphilis in 1932 and again in 1949; he was also said to have been a chronic alcoholic for about five to ten years with frequent episodes of delirium tremens. A physical examination for employment was reported as normal, and an insurance examination in 1944 was reported to have been acceptable. He was rejected from military service in 1945 for unknown reasons. The family history was negative.

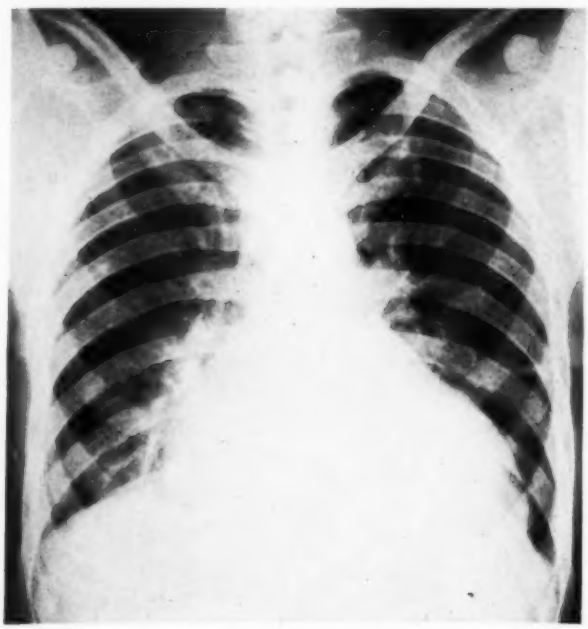


Fig. 10 (Case 9).—Roentgenogram of chest revealing moderate cardiac enlargement with a scar in the left lower lung due to previous pulmonary infarction.

The physical examination on the first admission to our hospital in January, 1951, revealed marked dyspnea and cyanosis. He was afebrile. The eye grounds were negative. There were a few moist râles in the lung bases. The heart rate was 110 to 120, and the rhythm was regular. The highest blood pressure recorded during this admission was 110/90 mm. Hg, and it remained persistently low. There was marked cardiac enlargement with poor heart tones, a low-grade, apical, systolic murmur, and an intermittent diastolic gallop. No pericardial friction rub was heard. The liver was enlarged and tender. Pedal edema was marked. The clinical impression was idiopathic hypertrophy of the heart with congestive heart failure.

Except for a positive blood Kahn test, the laboratory findings were negative. These included urinalysis, hemogram, and nonprotein nitrogen determinations. The chest x-ray examination and cardiac fluoroscopy revealed both left and right ventricular enlargement and a linear fibrotic area in the left midlung periphery (Fig. 10). The electrocardiogram revealed left ventricular hypertrophy (Fig. 11).

The patient improved rather promptly and was discharged on Feb. 14, 1951, with the diagosis previously stated. He was readmitted on March 10, 1951, with another bout of congestive heart failure and pain in the right chest and epigastrium. The temperature was 104.6° F., rectally, on admission. The blood pressure was 120/95 mm. Hg. The heart rate was 120, with a regular rhythm. There were dullness and moist râles in the right lung base posteriorly. There was a questionable pulsus paradoxus. No friction rub was found. The clinical impression was the same as before, with an additional complicating infarct in the right lung. A chest roentgenogram again revealed marked cardiac enlargement plus suggestive changes of a pulmonary infarct in the right cardiophrenic angle. The electrocardiogram revealed sinus tachycardia and left ventricular hypertrophy. Recovery was slow, and the patient was discharged on March 26, 1951. The patient is still living and is asymptomatic at the present time.

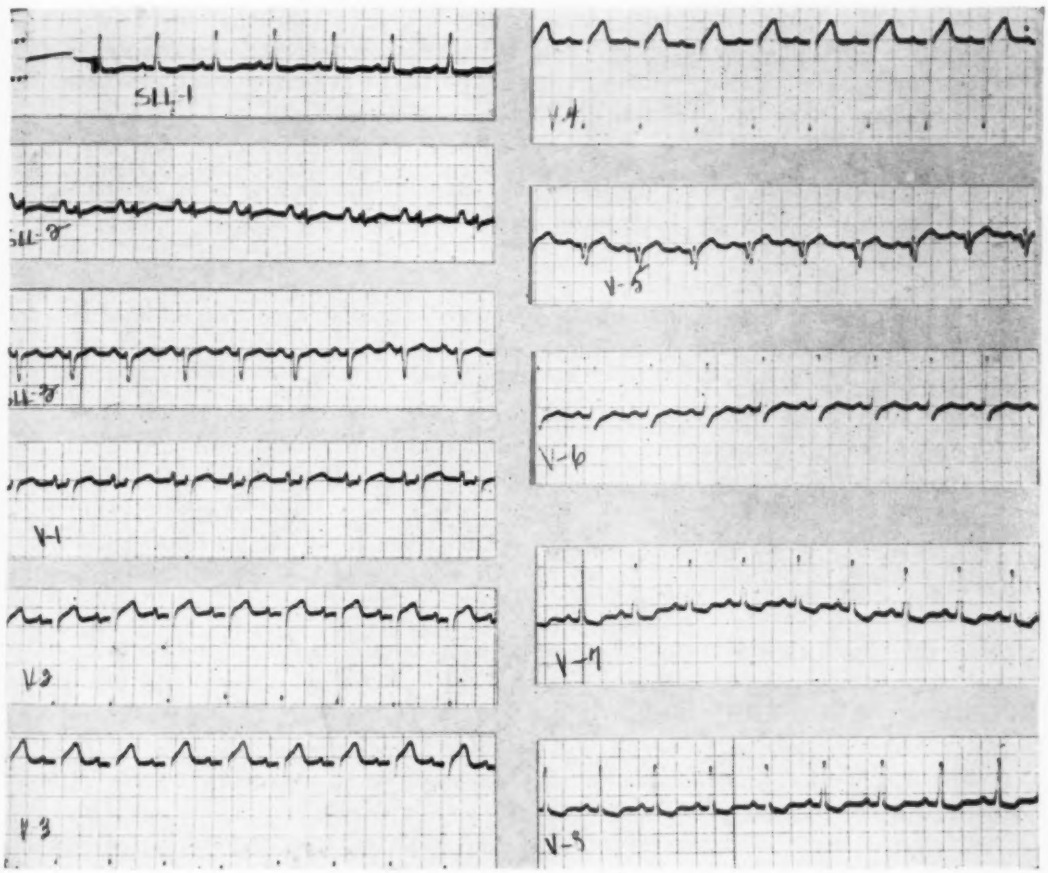


Fig. 11 (Case 9).—Electrocardiogram revealing left ventricular hypertrophy pattern.

ANALYSIS OF MATERIAL

The patients in this series ranged in age from 24 to 44 years; seven were male and two female. Seven of the nine patients were Negroes. In six cases palpitation, which was associated with an arrhythmia in two cases, seemed to be an early and major complaint. All patients had symptoms of congestive heart

failure when first seen by us. Of these patients, three had symptoms of pulmonary infarction early in the course of the disease. The duration of symptoms ranged from one to five years. Three patients survived over four years; one patient is still living two and one-half years after the onset of the illness, and one patient is living one year after the onset of illness. The findings on physical examination demonstrated signs of congestive heart failure in all instances. Seven patients had low pulse pressures during the course of illness, and one developed a low pressure during the terminal stage of illness. Five patients had diastolic gallop rhythm. All patients had cardiac enlargement, and this was marked in most instances. In five cases the systolic pressure was below 100 mm. Hg at some stage of the illness, usually terminally. All patients were afebrile except when the illness was complicated by embolic phenomena. In all cases the eye grounds were normal. Murmurs suggestive of the presence of valvular heart disease were present in two patients; however, the structural integrity of these valves at autopsy indicated that these murmurs were functional.

All roentgenograms of the chest demonstrated heart enlargement, according to the present standards of measurement. In most cases cardiac enlargement was marked. The left ventricle was found to be enlarged in six patients fluoroscopically. The heart silhouette was consistent with a large pericardial effusion in three patients: fluoroscopy revealed poor pulsation in two of these; pulsations in the third were of normal amplitude. In seven patients there were scars or infiltrations consistent with old or new pulmonary infarction. An analysis of the electrocardiograms demonstrated that there were four instances of left bundle branch block. Electrocardiographic evidence of paroxysmal auricular tachycardia was present in one case. In another there was auricular fibrillation during the terminal phases of the illness. In three cases there were nonspecific electrocardiographic changes, consisting of T-wave inversion and ST segment alterations, with absence of bundle branch block. Three patients had electrocardiograms compatible with left ventricular hypertrophy.

Six patients were examined at necropsy, and all presented the findings of cardiac hypertrophy, grossly and histologically, with absence of significant valvular or coronary artery disease. The parietal pericardium in one patient was thickened and adherent to surrounding pleura and underlying visceral pericardium. We feel that multiple pulmonary infarcts caused this finding. The myocardium demonstrated gross areas of myelomalacia in two cases. Histologically, changes of hypertrophy alone and with varying degrees of necrosis, fibrosis, and cellular infiltration were noted. Mural thrombi were observed in four patients.

DISCUSSION

In a five-year period of study of both clinical and post-mortem material, we observed nine cases of heart disease for which no etiological factor, or factors, could be found. In our attempts to determine the etiology of these cases of heart disease, an effort was made to exclude some of the more common causes of heart disease; namely, syphilis, previous hypertension, bronchopulmonary disease,

anemia, trauma, nutritional disturbances, amyloidosis, coronary artery disease, rheumatic fever, and pericarditis.

When these patients were admitted for study, many diagnoses were entertained. In several cases recurrent pericardial effusion of tuberculous or unknown etiology or chronic constrictive pericarditis were considered. This difficulty in differentiation arose because of the findings of congestive heart failure, low pulse pressure, pulsus paradoxus, distant heart tones, and the fluoroscopic and electrocardiographic findings. This presented a distinct difficulty in three of the cases reported and led to attempted pericardial paracentesis in two instances. Frank blood was obtained in both. A similar experience has been reported by others.[13] One patient died while being anesthetized for pericardial resection. In this case cardiac enlargement was not believed to be incompatible with constrictive pericarditis. In a series of fifty-three patients reported by Paul and associates,[14] enlarged cardiac silhouettes were found in the presence of constrictive pericarditis in 54.7 per cent. Roentgenkymographic and angiocardiographic studies had been performed in our case, and even these procedures did not exclude the possibility of chronic pericardial disease. In a case reported by Graybiel and White,[15] surgical exploration was undertaken in a case similar to ours. Cardiac enlargement was present, and post-mortem examination demonstrated diffuse myocardial fibrosis of unknown etiology.

Various authors[8-10,16] have made reference to myocarditis developing after antecedent infections and to subsequent cardiac hypertrophy and dilatation, but the evidence for this is not conclusive. There is certainly much less specific evidence than in the myocarditis associated with diphtheria, rickettsial, and viral diseases. As pointed out by von Bonsdorff,[1] in 1939, the data obtained in cases of heart disease of obscure origin are vague, ambiguous, and rarely convincing when considered against the background of the severe heart disease which these cases show. Conversely, in rheumatic fever, after recovery from acute rheumatic myocarditis, fibrosis and hypertrophy are uncommon unless there is resultant valvular deformity. It is difficult to assume that minor illnesses might result in such severe heart disease occurring months to years after the infection in a few individuals, yet a vast majority of persons suffering from the same diseases might be allowed to escape without cardiac sequelae. It is interesting to note in our series that the majority of patients complained initially of a "cold." Such a history might well lead to the presumption that an infectious illness preceded the onset of heart disease. Careful interrogation, however, revealed that these symptoms were actually those of incipient congestive failure.

The pathological changes observed in this series were those of hypertrophy with varying degrees of fibrosis and necrosis with or without cellular infiltration. In all the cases reviewed in the literature and in our own series, we believe that the observed pathological changes are ones of degree rather than of character. The degree of changes seems to bear no constant relation to the duration of the known clinical symptoms or to any known specific etiological agent. A review of several series of patients who clinically and pathologically were similar to those being reported was made. Pathologically, the myocardial changes varied from

hypertrophy alone to hypertrophy associated with severe fibrosis and necrosis.[1-4,13] It has been pointed out that hypertrophy may result in areas of necrosis which have been described pathologically in some cases as myocardial infarction in the absence of coronary thrombosis or embolism.[13,17] As Roberts and Wearn observed,[18] the increased muscle mass in cardiac hypertrophy may exceed the functional capacities of the capillaries, impairing tissue metabolism. That this may result in an ischemic myocardial necrosis is pointed out by Hull,[19] Friedberg and Horn,[17] and Gross and Sternberg.[20] Cellular infiltrations may be the result of congestive failure[21] or may be associated with ischemic necrosis. It is known that the histological picture, said to be due to inflammatory disease, may well be the result of a degenerative process initiated by cardiac hypertrophy.[13] Parenthetically, the exciting cause of hypertrophy is as obscure as are those exciting causes listed for so-called myocarditis with resultant hypertrophy of heart muscle.

In attempting to find factors which may be responsible, the authors conjecture that racial factors may be important. Seven of nine cases in our series occurred in young Negro adults. In comparing this incidence to the racial distribution in the hospital population, we find that the incidence is higher. Reisinger and Blumenthal[13] expressed a similar belief. Evans[22] has raised the question of familial incidence in cases similar to those that are being reported. In three of our cases there was a family history of "heart attacks" in early adult life.

The physiology of cardiac hypertrophy is poorly understood even when the exciting cause of hypertrophy, namely, lengthening of the muscle fibers, is present. The stimulus or stimuli for fiber lengthening are not apparent in our cases. In this series we believe that some stimulus or stimuli other than previous inflammation must exist to produce cardiac hypertrophy. It is unknown whether there is any similarity in the chain of events that led to hypertrophy in the cases reported here. The authors believe that attention should be directed to the study of other physiological factors in cardiac muscle hypertrophy, particularly in derangements of the metabolism of the heart muscle cell.

CONCLUSIONS

1. Nine cases of heart disease due to unknown cause have been observed in a five-year period.

2. A striking similarity in the clinical course and physical findings was present in all cases.

3. One chief problem in differential diagnosis was that of pericardial disease.

4. It is our impression that the histological findings observed in these cases are the result of degenerative changes in previously hypertrophied muscle rather than the sequelae of inflammatory disease with secondary hypertrophy.

5. Attention should be directed to the study of cardiac hypertrophy from the standpoint of cellular physiology.

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SYSTEMIC ARTERIAL EMBOLISM IN RHEUMATIC HEART DISEASE

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RHEUMATIC heart disease is an important cause of systemic arterial embolism. In 1933, Weiss and Davis[76] published a report on embolic episodes in rheumatic heart disease, using autopsy material as their source of study. Harris and Levine,[25] in 1941, reported on a series of cerebral emboli complicating rheumatic heart disease. In 1950, Bourne[6] published a report on the relationship of exertion to embolism in mitral stenosis. Recent publications (Warren and Linton,[75] Haimovici,[23] and Andrus[3]) on the general subject and the treatment of arterial embolism emphasized further the importance of rheumatic heart disease as an etiological factor.

The considerable progress in the past few years with anticoagulant agents as a protection against embolism and the recent surgical obliteration of the left atrial appendage as a possible focus of thrombus formation in rheumatic heart disease were responsible for the present study. It was undertaken primarily to elucidate the factors favoring intracardiac thrombosis, to ascertain the relative frequency of the atrial appendage as the offending site, and to appraise the results of therapy.

The records of 194 patients, including the autopsy findings in thirty-nine patients, were obtained from the Massachusetts General Hospital, the House of the Good Samaritan, and the private practice of two of the authors (E. F. B. and P. D. W.). The period covered was from 1923 to 1950. Patients suffering from bacterial endocarditis have been excluded.

CLINICAL FEATURES

Sex and Age.—There were 131 female and sixty-three male patients. The age at the time of the first embolic episode ranged from 7 to 74 years. The detailed age and sex distribution is shown in Fig. 1, which emphasizes the predominance of females and the maximum incidence in the fourth decade. Embolism

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occurring after the fifth decade is more often from intracardiac thrombi secondary to myocardial infarction or chronic atrial fibrillation in arteriosclerotic heart disease. Rheumatic heart disease, however, is not uncommon among the aged and may be complicated by embolism as shown by the autopsy study of Sprague and Carmichael.[64]

Sites of Emboli.—The sites of lodgment of the emboli are given in Table I. As has been previously stressed by Warren and Linton,[75] there is a considerable discrepancy between the clinical and autopsy diagnoses of visceral embolism. This discrepancy can be accounted for in several ways. For example, renal emboli have a notoriously variable symptomatology; many occur without the patient's knowledge, and few are accompanied by severe pain and massive hematuria. Hoxie and Coggin[31] found that a correct clinical diagnosis had been made in only two out of 205 renal infarctions. However, with the aid of special urological studies, a correct diagnosis can be made with greater frequency.[55] Confusion also frequently occurs between splenic, left renal, and pulmonary infarction.

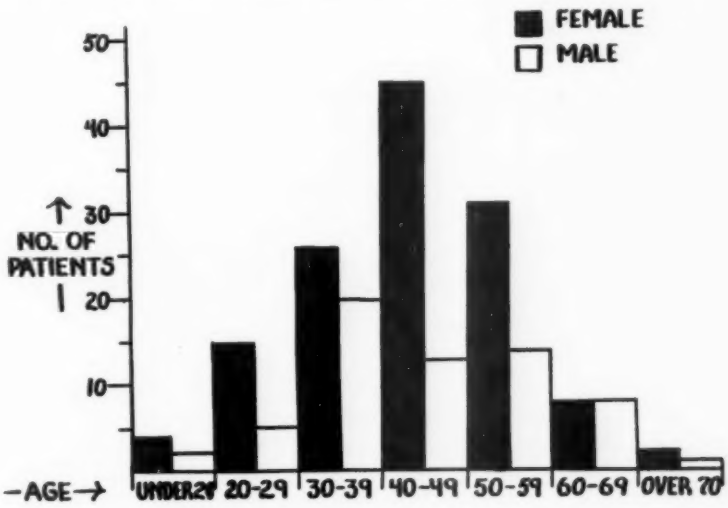

Fig. 1.—Age at time of first embolus.

Correlation between clinical and autopsy findings suggests that, although some visceral emboli are not silent, pain and discomfort may be so fleeting and varied that unless they are preceded or succeeded by major embolic events their significance is not recognized.

Cerebral emboli are usually overt, but even they may have few clinical manifestations, being represented by transient unconsciousness, motor or sensory dysfunction, or neurological features so bizarre that they are misdiagnosed.

It is well known that sterile emboli most frequently lodge at the bifurcation of the large arteries and tend to avoid small right-angle branches, such as the coronary and intercostal arteries. Embolism of small arteries, especially if multiple or repeated, suggests strongly the diagnosis of subacute bacterial endocarditis.

TABLE I. SITES OF LODGMENT OF 393 EMBOLI OCCURRING IN 194 PATIENTS

SITE		NUMBER	PER CENT
Arteries to the brain		188	47.8
Cerebral	182		
Carotid	2		
Basilar	1		
Retinal	3		
Arteries to the abdominal viscera		56	14.2
Mesenteric	11		
Splenic	17		
Renal	28		
Aortic bifurcation		23	5.9
Iliac arteries		21	5.3
Arteries to the lower extremities		66	16.8
Femoral	29		
Popliteal	21		
Tibial	16		
Arteries to the upper extremities		39	10.0
Axillary	3		
Brachial	36		
Total		393	100

Episodes and Intervals Between Episodes.—The occurrence of one or more emboli in a twenty-four hour period was considered to be one episode. By this arbitrary definition, there were seventy-nine patients who had single, and 115 who had multiple, episodes varying from two to six in number. Sixty-four patients had two episodes, twenty-eight had three, thirteen had four, six had five, and four had six.

The interval between episodes varied from one day to eleven years. Fig. 2 shows that while the majority of episodes occurred within six months of each other, a significant number were separated from six months to five years.

PREDISPOSING FACTORS TO EMBOLISM IN RHEUMATIC HEART DISEASE

A. Valvular Involvement.—The type of valvular lesion present in 194 patients, as determined clinically in 155 and at autopsy in 39, is listed in Table II.

TABLE II. THE TYPES OF VALVULAR LESIONS IN 194 PATIENTS

VALVULAR LESIONS	NUMBER
Mitral stenosis	50
Mitral regurgitation	3
Mitral stenosis and regurgitation	62
Mitral and aortic valvular disease	62
Mitral and tricuspid valvular disease	5
Mitral valvular disease and atrial septal defect	1*
Mitral, aortic, and tricuspid valvular disease	5
Aortic valvular disease	5
Aortic stenosis and constrictive pericarditis	1*

*Confirmed at autopsy.

The mitral valve was involved in 188 patients (97 per cent). In six patients the aortic valve alone was diseased; the essential lesion in five was aortic stenosis and in the other aortic regurgitation. One patient with aortic stenosis had, in addition, an "external pressure" stenosis of the mitral valve by a penetrating calcific plaque.

B. Arrhythmias.—One hundred and seventy-four patients (90 per cent) had atrial fibrillation, and two had atrial flutter. Eighteen patients, so far as can be ascertained, did not have fibrillation at the time the emboli occurred, but they were not all observed at the exact time of the episode, and it is possible that some of them had paroxysmal fibrillation.

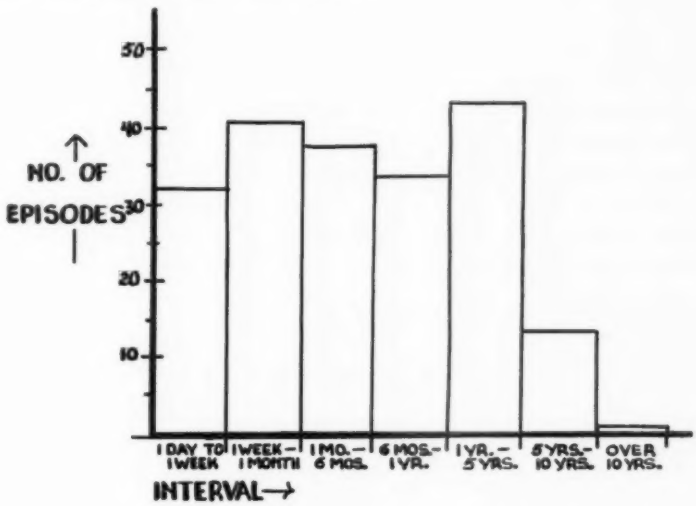

Fig. 2.—The time interval between episodes.

The duration of atrial fibrillation before the first embolic episode was known in eighty-three patients. Eight had paroxysmal fibrillation, eighteen had had fibrillation for less than one month before the onset of the first embolus, and in seven the onset of fibrillation was probably concurrent with the embolic incident. The remainder had had fibrillation for one year or longer, many for over ten years.

C. Heart Size.—There was x-ray evaluation of heart size in eighty-five patients; in fifty-two there was moderate enlargement. The enlargement was mainly of the left atrium and varied from slight to moderate in degree. Great left atrial enlargement was less common, although one patient had a giant atrium which at autopsy had a capacity of over 1,000 c.c. Embolism is uncommon in patients with giant left atria.[14]

D. Drugs.—One hundred and twenty-seven patients were receiving digitalis at the time of the first or subsequent episodes. Most had been taking digitalis for years prior to the first embolus, but six patients had been receiving it for less than one week, and in one instance the dose was excessive. There was no evident relationship between digitalis therapy and embolism.

Eleven patients had at some time been given quinidine. In eight of the eleven, including one patient who was successfully converted to normal rhythm, there was no relationship between embolism and quinidine therapy. The remaining three patients received quinidine eight days, two days, and one day, respectively, before embolic episodes, but only one was temporarily restored to normal rhythm. The use of quinidine in restoring normal rhythm has been suspected of precipitating embolic episodes.[15,21,77] Other workers, however, notably Sokolow,[62,63] have minimized such dangers. The use of quinidine in this series was too limited for critical evaluation, but the evidence supports the latter view.

E. Congestive Failure.—As judged by usual clinical standards, forty-one patients had mild, four moderate, and twenty-four severe congestive failure at the time of the first embolic episode. In these sixty-nine instances there was no correlation between the duration of failure and the onset of embolism or between the severity of failure and the number of emboli. Furthermore, the severity of failure did not appear to influence the degree of ischemia after an embolus had lodged in a limb artery.

F. Other Predisposing Factors.—Physical exertion did not influence significantly the occurrence of emboli. In fact, more emboli occurred when the patient was in bed asleep or physically inactive than when he was strenuously exercising. This coincides with the findings previously noted by Sprague and Westinghouse[65] and Bourne.[6] The position of the body did not seem to influence the location of an embolus, and there was no undue proportion of cerebral emboli when the patient was recumbent.

Surgical operations and pregnancy did not immediately precede or accompany embolism in a significant proportion of patients.

Hypertension was more common in older patients, but the incidence did not exceed that in nonrheumatic patients and did not influence embolus production. Twenty-one patients had febrile infections, mainly upper respiratory, within two weeks prior to embolism. The role of active rheumatic infection is discussed only in patients who were autopsied because of the vagaries of clinical diagnosis.

POST-MORTEM DATA

Thirty-nine patients in this series were autopsied. There was no left atrial enlargement in ten, slight in eleven, moderate in fifteen, great in two, and in one case the left atrium extended as far as the right chest wall.

Intracardiac thrombi were found in twenty-five of the thirty-nine patients. The locations of the thrombi in these twenty-five patients are given in Table III. In the fourteen instances where no thrombus was found, there was a roughened area on the posterior atrial wall in five, and a similar area on the side of the atrial septum in another. These areas appeared to represent the site of a previous thrombus. One of the atrial thrombi was a ball thrombus lying free in the cavity. Another was a true paradoxical embolus which was lodged in a patent foramen ovale, but in this case there was further thrombus formation on the posterior atrial wall. Most atrial thrombi were situated on the posterior wall

just superior to the mitral valve in the region where MacCallum's patch occurs, and three thrombi, while having their main attachment to this area, almost filled the atrium and spread into the mouths of the pulmonary veins.

TABLE III. LOCATION OF THROMBI FOUND AT AUTOPSY IN 39 PATIENTS

LOCATION	NUMBER
Cavity of left atrium	11
Appendage of the left atrium	10
Cavity and appendage, left atrium	4
No evident origin	14

In one case the embolic source consisted of calcified plaques on a stenotic aortic valve, similar to a case reported by Zak and Elias.[82] Fracture lines could be seen along the free valve border, and the emboli were calcific in nature. There was also mitral stenosis in this case, but no atrial thrombus was present. It is interesting that this patient had emboli to both central retinal arteries before a terminal superior mesenteric embolus occurred.

Two patients with aortic stenosis without mitral stenosis were autopsied. In one the mitral ring was calcified, and there were two red plaques on the posterior wall of the left atrium, together with considerable fibrosis of the wall in the same region. The left atrium was a little larger than normal. The other had calcification which had progressed to bone formation at the base of the mitral valve, but there was a thrombus in the appendage.

Histological evidence of active rheumatism was found in nine of the thirty-nine autopsy patients, and in only one of the nine was there no thrombus. The incidence of active rheumatism in the series is lower than that reported by others, but it may well be accounted for by different criteria for diagnosis. However, fibrosis of the wall of the left atrium was extensive in an additional eleven cases. Usually, thrombi occurred in the vicinity of the greatest fibrosis.

All the patients having extensive atrial thrombi had atrial fibrillation before death, a higher incidence than recorded by others.[12,19,22,26,28,61,69,76]

PROGNOSIS

Of the 194 patients, 137 (71 per cent) are known to be dead, fifty-five (28 per cent) are known to be living at the present time, and two (1 per cent) are lost. Of the 137 dead, twenty-three died shortly following, and as a direct result of, one embolic episode. Of these, fifteen died of cerebral embolism, and eight died of embolism of the aorta or its major visceral branches, five with emboli in the superior mesenteric arteries, and three with emboli at the aortic bifurcation, one of whom had bilateral renal emboli. Twenty-nine patients who survived one episode died subsequently from nonembolic causes, usually within several years but as late as twelve years afterward.

Of the remaining eighty-five known dead, fifty-five died of further embolic episodes. Of these, forty-nine died of cerebral emboli, five of superior mesenteric

emboli, and one of renal emboli. Twenty-four died of cardiac failure, seventeen of whom had complicating pulmonary embolism. Six died of miscellaneous causes.

Thus, seventy-nine patients out of the total of 192 (41 per cent) who could be followed died as a result of the first or a subsequent embolus. Sixty-four of the 192 (33 per cent) died of cerebral emboli. Of the remaining fifteen, ten died of superior mesenteric emboli, two of rider emboli, two of bilateral renal emboli, and one of a ball-valve thrombus in the mitral orifice.

In an attempt to trace the fate of patients who survived the first episode, a follow-up study was made of those in whom the initial episode occurred prior to 1940. This has provided a follow-up of a minimum of ten years, or to death, with a longest follow-up of nineteen years. The results are shown in Fig. 3, in which deaths from emboli and other causes are shown.

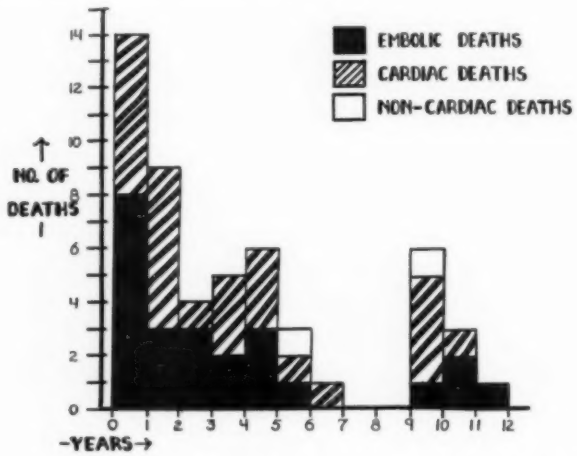

Fig. 3.—Fate of patients who had the first embolus between the years of 1922 and 1940 (six living; two lost).

FEATURES OF EMBOLI IN VARIOUS SITES

A. Central Nervous System.—Harris and Levine,[25] in 1941, reported the findings in seventy-two patients suffering from cerebral embolism and mitral stenosis. In their series the immediate mortality was 33 per cent. In the present series, which includes all forms of rheumatic heart disease, 130 out of 194 patients had one or more episodes of cerebral emboli, and sixty-four of the 130 (49 per cent) died as a result of this complication. The central nervous system is the most frequent and most dangerous site for emboli to lodge. Not only is the mortality high, but in those who survive, the residuals are often severe and crippling. Many have persistent motor disability, aphasia, and mental deterioration. One patient, following a right cerebral embolus, developed a condition resembling a painful myostatic dystonia of the left arm, requiring unilateral lobotomy for the relief of pain (Stafford-Clark[68]).

These complications interfere with social and economic recovery, tragically so in those who otherwise have little cardiac disability. More optimistically, a

minority of patients make a remarkably complete and rapid recovery from what initially appeared to be a severe cerebral disturbance. One 32-year-old man recovered sufficiently from a hemiplegia to work for five years in a factory before dying of pneumonia. Autopsy revealed an extraordinary degree of cerebromalacia. Occasionally, patients in cardiac failure are temporarily improved by the advent of an embolic hemiplegia, but the explanation is not clear, unless more complete rest is the answer.

As might be expected from the anatomy of the aortic arch, emboli travel with greater facility up the right than the left carotid arteries, and hence left hemiplegias are more common than right.

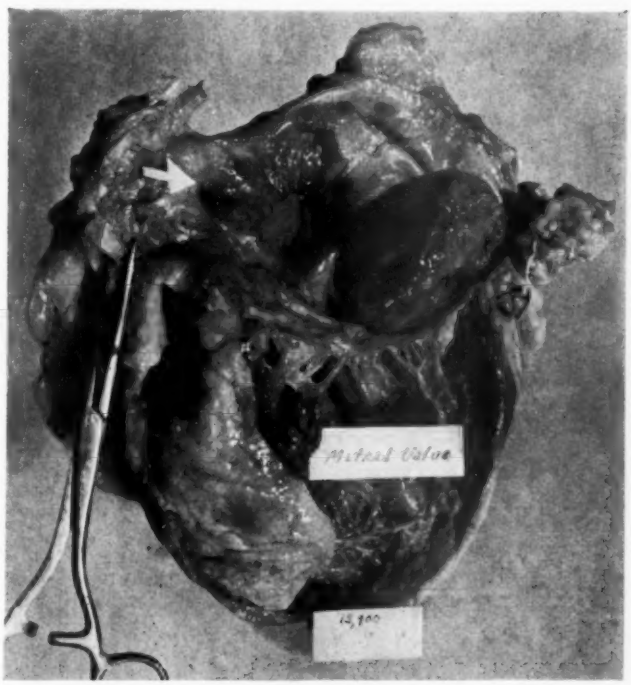

Fig. 4.—Ball-valve thrombus obstructing the mitral orifice.[9]

There is no satisfactory treatment of cerebral embolism. In recent years various attempts have been made to improve the collateral circulation and limit the area of infarction by blockage of the stellate ganglion.[2,11,20,37,43,74] The most promising report is by Gilbert and deTakats[20] who blocked the stellate ganglion of ten such patients and considered that there was immediate improvement in all. However, Scheinberg,[60] in a careful study of cerebral metabolism and blood flow before and after stellate block in patients suffering from cerebral apoplexy, found no alteration in either function and hence doubted that stellate block could be effective. In our series, two patients with cerebral emboli had stellate blocks, one repeated without any dramatic results. Anticoagulants are considered by many to be too risky under these circumstances, but further experience is necessary. A preliminary report has been recently made by Foley and Wright.[17]

B. The Aorta and Its Branches.—Higher degrees of stenosis of the mitral valve tend to limit the size of the emboli eventually liberated into the arterial tree, but autopsy studies often show that a surprisingly large embolus has passed through a severely stenotic mitral orifice. Occasionally, large thrombi remain free in the atrial cavity, or on occasion a ball-valve thrombus intermittently and finally permanently obstructs the mitral orifice, resulting in death. One such case occurred in our series[7] (Fig. 4), and again in another patient with rheumatic heart disease who was not included in the present study since the patient had an associated subacute bacterial endocarditis. There was no instance in the present series of lodgment of an embolus in the thoracic or abdominal aorta except at the bifurcation of the latter (rider or saddle embolus). Lodgment in the main divisions of the thoracic aorta or its smaller branches, such as the coronaries, intercostals, and internal mammaries, did not occur in the present series. Embolism to other branches of the abdominal aorta, on the other hand, did occur with lodgment in the mesenteric artery in eleven instances, in the splenic arteries in seventeen, and in the renal arteries in twenty-seven. Embolism to the mesenteric arteries had the highest mortality, as death occurred in ten out of eleven patients, and in the one who survived, the diagnosis may have been in error. A similar high mortality has been reported by others.[31,57,71] Fatal embolism to the kidneys occurred in two instances.[8,9] There were bilateral emboli resulting in massive infarction, and in one case these were accompanied by a rider embolus at the bifurcation of the aorta which was successfully removed before death occurred from the renal failure. In one instance arterial hypertension and impairment of function of one kidney followed the clinical diagnosis of renal embolism; otherwise, no serious complications arose. Emboli to the spleen were nonfatal. The importance of splenic infarction lies chiefly in its differentiation from infarction of the left lung or kidney.

Pronounced abdominal pain, nausea, and vomiting were present in three patients with embolism at the bifurcation of the abdominal aorta, and in two instances the patients were under observation for an acute attack of gall bladder disease before the signs of embolism became obvious. Similar abdominal symptoms of a milder character and greater variability occurred in other patients with embolism to the aortic bifurcation or iliac arteries. The exact cause of such symptomatology is unknown, but it has previously been noted by Herrmann and associates.[29] It has been suggested that it represents migration of a large embolus down the abdominal aorta, but associated occlusion of small visceral arteries by showers of smaller fragments cannot be excluded.

The bifurcation of the abdominal aorta into the two common iliac arteries of smaller caliber but with little change in the direction of the blood flow provides an ideal location for the lodgment of a large embolus. This lodgment at the bifurcation may be only temporary. From this site migration or propagation may occur to one or both iliac or femoral arteries or to smaller distal branches in the lower legs. At times it may be impossible to differentiate bilateral iliac embolism from a rider embolus. In the total of forty-six instances of lodgment in these two locations, embolectomy was performed seventeen times, and in the entire group

amputation of one or both legs was performed eight times. Death occurred too soon after the development of the embolus to determine the outcome of the ischemia in three instances. Five of the amputations were performed because of gangrene which developed after embolectomy. The interval between the development of symptoms and embolectomy in three of the five patients was eighteen hours, twenty-four hours, and slightly over twenty-four hours, respectively. In the two remaining the time interval was not recorded. Three of the patients had cardiac failure of a serious degree. The twenty-nine patients not having embolectomy had varieties of treatment, as methods changed between 1922 and 1950, and those surviving without gangrene all had chronic arterial insufficiency of some degree. During the period from 1940 to 1950 the clinical diagnosis of rider embolus or emboli to the iliac arteries was made much more frequently than in the preceding fifteen-year period from 1925 to 1940, probably because of an increased awareness of the seriousness of the condition, which resulted in earlier hospitalization. This is borne out in recent publications.[1,21,56,75,78,79]

Emboli to the aortic bifurcation have a very serious prognosis. It is here that the most dramatic results of early embolectomy (preferably within eight hours) are seen. Particular attention should be given to the possibility of further emboli in the iliac and femoral arteries, and anticoagulant therapy can do much to reduce distal propagating thrombi.

Superior mesenteric arterial embolism has a very grave prognosis, and in this series ten out of eleven died. Every effort should be made to make the diagnosis early, perform the necessary resections, however extensive, and supplement with postoperative anticoagulant therapy.

C. Arteries of the Extremities.—Embolism to the arteries of the lower extremities occurred sixty-six times in the series, most commonly to the femoral arteries. Embolectomy was performed eight times. No gangrene occurred in the patients having embolectomy, but there were nine amputations performed because of gangrene in the remaining patients treated by other methods.

Embolism to the arteries of the upper extremities occurred thirty-nine times in the series, in three instances to the axillary and in thirty-six instances to the brachial arteries. Embolectomy was performed once for an axillary embolus and six times for brachial emboli.

One patient with an embolus to a brachial artery received no specific therapy for three days before admission to the hospital and subsequently developed forearm gangrene which necessitated amputation of the arm. There was no unusual feature about this patient apart from a hemiplegia on the same side, due to a concurrent cerebral embolus. This was the only upper extremity lost in the series.

Warren and Linton,[75] in 1948, reviewed the surgical experience in peripheral arterial embolism from all causes at the Massachusetts General Hospital. There have been the recent reviews of Andrus,[3] Haimovici,[23] and others.[18,27,33,45,46,49,58,72] In general, the prognosis following embolism of the upper limb is good, whatever method of treatment is used. However, in order to minimize the possibility of chronic ischemia, most authors recommend embolectomy for axillary and brachial emboli, if the patient is seen within ten hours of onset, followed by anticoagulant

therapy to reduce the secondary thrombus which so commonly occurs distal to the embolus. If embolectomy is impractical, improvement will probably be obtained by repeated upper thoracic sympathetic blocks, but such should not be made concurrently with anticoagulant therapy as extensive hemorrhage and hematomas may occur as a complication.

Femoral emboli if seen within eight to nine hours are favorable for removal, and on occasion even later embolectomy has produced good results. Other forms of "conservative" treatment should be added when necessary including lumbar sympathetic block, intermittent venous occlusion, and the oscillating bed. Most authors, including Warren and Linton,[75] agree that the technical difficulty of removing popliteal emboli is so great that conservative measures are preferable.

Thus, with the exception of popliteal emboli, early embolectomy followed by anticoagulants is the ideal treatment, and, whatever form of treatment is used, the results in the upper limbs will always be superior to those in the lower. That arterial spasm distal to an embolus is a major cause of secondary thrombus formation has been emphasized by Linton[39] and others. Association of venous spasm and thrombosis was pointed out by McKechnie and Allen,[47] and there is accumulating evidence that this is of some importance, especially in the legs. Micrometric studies by Laufman and co-workers[36] have established the existence of accompanying vasospasm in main-stem vascular occlusions. These observers found that in arterial occlusion there is a marked arterial spasm and a concomitant venous spasm. In venous occlusion they observed a marked arterial spasm and a venous dilatation. Haimovici[23] found an incidence of concurrent venous thrombosis of 7 per cent or twenty-four of 330 cases of peripheral arterial embolism. He considered the important mechanism in such instances to be a transverse propagation of the inflammatory process from the arterial wall to the adjacent vein. In our series, nineteen patients had one or more pulmonary emboli shortly following arterial emboli to the legs. If this association is borne out by other observers, anticoagulant therapy becomes of increasing importance, and even routine prophylactic vein ligation may need consideration at the time of embolectomy.

Congestive failure and shock if present should, of course, receive vigorous treatment to increase the cardiac output and improve the general circulation. In the treatment of congestive failure care should be taken to avoid a too vigorous diuresis, as Pere[54] has recently shown that such may enhance the development of further thromboembolism. The concomitant use of anticoagulants during treatment of congestive failure in such patients is therefore indicated for this additional reason.

PROPHYLAXIS OF RECURRENT EPISODES

Once a patient has had one embolic episode, the aim of treatment should be to eradicate the source of the embolus and to prevent further intracardiac thrombus formation. Various attempts, notably by Madden[44] and by Baronofsky and Skinner,[5] have been made to remove one possible source by amputation or ligation

of the left atrial appendage, but the autopsy material reported here is somewhat discouraging since the appendage alone contained a thrombus in only ten out of thirty-nine cases. Since atrial fibrillation has been found to be present in the majority of the patients who are found to have intra-atrial thrombi and embolic episodes, numerous attempts have been made at conversion to and maintenance of normal sinus rhythm by the use of quinidine sulfate.[21,48,53,62,61,71] Such conversion is not always possible; it is difficult to maintain normal rhythm in a patient with advanced mitral disease, and the frequent changes in rhythm themselves may favor the liberation of emboli in a heart that contains intracardiac thrombi. The long-term use of anticoagulants as a prophylactic measure against recurrent intracardiac thrombus formation is being studied by numerous observers at the present time.[13,16,30,32,80,81] The majority of the reports are encouraging, but technical difficulties are considerable. Criteria as to dosage of the anticoagulant, effective level of prothrombin activity, frequency of blood examinations compatible with safety, and duration of treatment are being assembled. Experience so far indicates that therapy must be continued indefinitely if protection is to be expected. Cosgriff[11] recently reported favorable results in seventeen patients who had a combined total of more than 200 months of anticoagulant therapy without serious hemorrhages or untoward effects. Sprague and Jacobson[66,67] have one patient who had had frequent emboli and who has now been under treatment for over three years without recurrence of emboli. In a similar long-term use of anticoagulants in the prophylaxis of recurrent coronary thrombosis by Nichol and Borg,[51] major hemorrhagic episodes occurred in thirteen of seventy-eight patients and were fatal in two patients. They believe that considerable further study and observation are necessary to determine whether or not the long-term use of an anticoagulant justifies the trouble and risk involved. In our series, five patients have been on long-term anticoagulant therapy (Dicumarol); the longest term is eighteen months. Four have been free from further emboli. One patient had an embolic recurrence two months after treatment began, even though the prothrombin activity was reduced to a presumable therapeutic level.

Long-term anticoagulant therapy may, therefore, have a place with intelligent patients and good laboratory facilities. To support this treatment, it is desirable to omit, if possible, drugs which may decrease the coagulation time. Relevant drugs which have been under suspicion include methylxanthines[40,59] and antibiotics.[50] However, more recent studies of the influence of aminophylline on the prothrombin time by Overman and Wright[52] and the effect of antibiotics on blood coagulation by Macht and Farkas,[41,42] and Lasser and associates[35] minimize such effects.

The contradictory reports on the effects of digitalis preparations on blood coagulation[10,24,38,70] have been clarified by the recent work of Pere,[54] who has shown that the effects of such digitalis preparations, as well as of mercurials, were in close direct relationship to the amount of diuresis produced by the administration of these drugs. He showed that if there was no diuresis from these drugs, blood coagulation was unchanged. In other words, the effect was not directly by the drugs, but as a result of the effect of the drugs in inducing diuresis and hemoconcentration.

In view of the fact that the combination of mitral valvular disease and atrial fibrillation seems so strongly to predispose to intracardiac thrombus formation, it is intriguing to speculate on the possibility of more radical forms of treatment. The possibilities that come to mind are an attempt at reversion to normal rhythm with quinidine after a period of anticoagulant therapy and surgical alleviation of mitral stenosis. In the latter connection it is becoming increasingly obvious that a preoperative assessment of the presence or absence of intra-atrial thrombi is of great importance. Arendt and Cardon[4] have made radiological examinations in an attempt to do this. The introduction of an instrument or finger into an atrium containing a thrombus may well dislodge emboli, and an otherwise successful operation may be marred by a hemiplegia or a fatal embolic episode.

SUMMARY AND CONCLUSIONS

The clinical features of 194 patients with rheumatic heart disease complicated by systemic embolism, with post-mortem studies in thirty-nine, have been reviewed to elucidate the factors favoring the intracardiac thrombosis, to ascertain the frequency of the atrial appendage as the offending site, and to appraise the results of therapy.

A mitral lesion was present in 97 per cent of the patients and atrial fibrillation in 90 per cent. Either mitral valve disease or atrial fibrillation was present in 100 per cent of the patients.

In a majority of instances, embolic episodes occurred during chronic atrial fibrillation in patients who were on maintenance doses of digitalis. A few occurred during bouts of paroxysmal fibrillation or during the time of onset or offset of this arrhythmia. There was a possible relationship of embolism to quinidine administration in only one patient.

Thirty-five per cent of the patients had congestive failure at the time of the first episode. There was no significant relationship between the incidence of embolism, the state of physical activity, surgical procedures, or the level of blood pressure.

There was histological evidence of active rheumatic disease at autopsy in nine out of thirty-nine patients.

Intracardiac thrombi were found at twenty-five of the thirty-nine autopsies. A thrombus was located in the cavity of the left atrium in eleven, in the atrial appendage in ten, and in both the cavity of the atrium and appendage in four.

Of a total of 393 emboli occurring in patients whose ages varied from 7 to 74 years at the time of first embolus, 48 per cent were to the brain, 14 per cent to the arteries of the abdominal viscera, 11 per cent to the aortic bifurcation and/or iliac arteries, 17 per cent to the arteries of the lower extremity, and 10 per cent to the arteries of the upper extremity.

Seventy-nine patients had single embolic episodes with an immediate 30 per cent mortality. One hundred and fifteen had multiple embolic episodes, and to date fifty-five have died of subsequent episodes. Fifty-eight have died of nonembolic causes. Of those who survived one episode, the highest mortality from embolic and nonembolic causes was in the first year, but fatal emboli continued to occur ten years or more later. A few survived over ten years.

Approximately 50 per cent of all emboli were cerebral in location with almost a 50 per cent mortality. Mesenteric embolism is much less frequent than cerebral but carries a higher mortality. There were only two deaths and eighteen amputations out of 129 emboli to the arteries of the limbs and the aortic bifurcation which is a lower mortality for life and limb than is seen in published reports of emboli from all causes.

Early recognition, prompt embolectomy in suitable patients, and anticoagulants have considerably improved the outlook for systemic emboli to the aortic bifurcation and extremities. There is no treatment as yet which has materially improved the prognosis of cerebral embolism.

The prophylaxis against recurrent embolism has been discussed.

ADDENDUM

Since the preparation of this paper, the results of a clinicopathologic study of fifty-one cases of mitral stenosis with intra-atrial thrombi have been published (Jordan, R. A., Scheifley, C. H., and Edwards, J. E.: Mural Thrombosis and Arterial Embolism in Mitral Stenosis, Circulation **3**:363, 1951). The findings and conclusions given by the authors were similar to ours in that only one-half of the mural thrombi in the left atria were found in the appendages, and they were of the opinion that surgical obliteration of the appendage would probably offer no more than a 50 per cent chance of eliminating the source for systemic arterial emboli. They likewise found a high incidence of atrial fibrillation, as forty-two out of fifty patients having mural thrombi in the auricles had this arrhythmia.

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SULFHEMOGLOBINEMIA: A STUDY OF 62 CLINICAL CASES

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SULFHEMOGLOBINEMIA and methemoglobinemia are two relatively uncommon conditions caused by the accumulation of abnormal amounts of sulfhemoglobin or methemoglobin in the blood.

Methemoglobin is a product of hemoglobin in which the normal ferrous complex is converted by oxidation to the ferric form.[1,2] Since methemoglobin does not combine with oxygen, it is of no value in respiration and hence must be considered temporarily inert.[3] Methemoglobin, however, is readily converted back to hemoglobin by reducing agents, and this is accomplished without associated damage to the erythrocytes. From 0.03 to 0.13 Gm. of methemoglobin per 100 c.c. has been found in the blood of normal persons.[4] The hemoglobin-methemoglobin equilibrium and the physiological effects of methemoglobinemia have recently been reviewed by Finch.[5]

While methemoglobin is a blood pigment occurring in normal persons in small amounts, sulfhemoglobin is an abnormal pigment not found in the body in ordinary circumstances.[5] The exact chemical nature of sulfhemoglobin is still unknown. It has been suggested that its formation involves the introduction of one atom of sulfur into the hemoglobin molecule and also a change in the mode of linkage of globin to heme.[3] Whatever its chemical nature, the result of this chemical union is a nonreversible product, that is, sulfhemoglobin, which remains until the erythrocytes containing it are destroyed.

Sulfhemoglobin is readily identified by its spectrum which shows a strong band at 618 mμ. The dark band of methemoglobin is seen at 630 mμ. The latter band disappears immediately after two or three drops of 5 per cent solution of potassium cyanide are added to the blood, and this test serves to differentiate it from sulfhemoglobin which remains fixed.[1,6]

Except for the extremely rare cases of so-called enterogenous sulfhemoglobinemia and primary or congenital methemoglobinemia, the occurrence of either of these pigments in abnormal amounts can be traced to amino and nitro compounds (Table I). Nitrites, sulfonamides, and aniline derivatives are the drugs which most commonly cause methemoglobinemia.[5] Phenacetin and acetanilid are the drugs most frequently mentioned as causative agents in the production

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of sulfhemoglobinemia, especially when it is associated with constipation or ingestion of sulfur-containing medicaments.[7,8] Whitby and Britton[9] stated that "constipation is invariable."

TABLE I. AMINO AND NITRO COMPOUNDS PRODUCING METHEMOGLOBINEMIA AND SULFHEMOGLOBINEMIA
(FROM FINCH[5])

AROMATIC DRUGS	ALIPHATIC AND INORGANIC DRUGS
Aniline	Sodium nitrite
Anilinoethanol	Hydroxylamine
Phenacetin	Dimethylamine
Acetanilid	Nitroglycerin
Methylacetanilid	Amyl nitrite
Hydroxylacetanilid	Ethyl nitrite
Prontosil	Bismuth subnitrate
Sulfanilamide	Ammonium nitrate
Sulfapyridine	Potassium nitrate*
Sulfathiazole	
Phenylenediamine	
Aminophenol	
Toluenediamine	
Alphanaphthylamine	
Paraminopropiophenone	
Phenylhydroxylamine	
Tolylhydroxylamine	
Nitrobenzene	
Dinitrobenzene	
Trinitrotoluene	
Nitrosobenzene	
Paranitraniline	

*Most frequent nitrate compound causing methemoglobinemia in our patients.

The clinical recognition of these abnormal states is dependent primarily on recognition of the cyanosis which is usually present, on a history of ingestion of drugs known to produce this state, or on both. The cyanotic state, in addition to such well-recognized causes of cyanosis as erythremia and certain types of cardiac and pulmonary disease, should always suggest the possibility of abnormal blood pigments. The absence of dyspnea, erythremia, and signs of cardiac or pulmonary disease should lead to spectroscopic examination of the blood.[3]

The presence of 5 Gm. of reduced hemoglobin per 100 c.c. of blood has been widely quoted as the amount of reduced hemoglobin necessary to cause clinical cyanosis;[10] however, recent studies have shown a wide variation in this figure.[11] A concentration of 1.5 Gm. of methemoglobin and of less than 0.5 Gm. of sulfhemoglobin has been stated to have effects comparable to those of 5 Gm. of reduced hemoglobin.

MATERIALS AND METHODS

An evaluation of the clinical state of patients who were given the diagnosis of sulfhemoglobin at the Mayo Clinic from May, 1939, to February, 1950, was undertaken by a study of the records. In each case the diagnosis was based on the results of spectroscopic examination of the blood.

Spectroscopic tests of the blood for sulfhemoglobin and methemoglobin were requested on 351 patients during this period. More tests than this were actually performed since repeated tests were made in some cases in following the course of the condition. In 131 of the 351 cases in which tests were made, results were positive; in forty-nine, tests were positive for methemoglobin and in eighty-two for sulfhemoglobin. In the forty-nine cases of methemoglobinemia the etiologic factors were sulfonamide drugs, nitrates from well water used in making infants' formulas, and potassium nitrate used for diuretic purposes.

In sixty-two of the eighty-two cases of sulfhemoglobinemia the records pertaining to this condition were sufficiently detailed for study and form the basis of this report.

RESULTS

The drugs which these sixty-two patients had taken are listed in Table II.

Concentration of sulfhemoglobin varied from 0.25 to 10.0 Gm. per 100 c.c. of blood. The symptoms for which the medicaments were administered are listed in Table III.

TABLE II. DRUGS TAKEN

DRUG	CASES	PER CENT
Bromo-Seltzer	38	61.4
Unknown	9	14.5
Acetanilid	6	9.7
"B. C."*	2	3.2
Sulfonamide	2	3.2
Phenacetin	1	1.6
A. P. C.*	1	1.6
Empirin*	1	1.6
Anacin*	1	1.6
Stanback*	1	1.6
Total	62	100.0

*All contain aspirin, phenacetin, and caffeine.

It was apparent from this study that a large percentage of these patients were neurotic individuals. This is evidenced by the high incidence of tension headache in this group. Two of the group were confirmed opiate addicts, and a number were thought to be psychologically dependent on potassium bromide, acetanilid, and caffeine (Bromo-Seltzer).

Constipation was a complaint of only twenty-six of these sixty-two patients. This finding is in marked variance with reports in the literature in which the presence of constipation has been greatly emphasized as an important and essential feature of sulfhemoglobinemia. Whether it is a causative factor or a result is debatable. This difference may be more apparent than real, however. In this group of sixty-two patients, fourteen patients had 2 Gm. or more of sulfhemoglobin per 100 c.c. of blood, and forty-eight patients had less than 2 Gm. of sulfhemoglobin per 100 c.c. of blood. Eleven of the fourteen patients who had

values of sulfhemoglobin of 2 Gm. or more were constipated, whereas only fifteen of the forty-eight patients who had lower values were constipated.

Cyanosis was detected on examination of all fourteen patients who had 2 Gm. or more of sulfhemoglobin per 100 c.c. of blood and of thirty-three of the forty-eight patients who had less than 2 Gm. of sulfhemoglobin per 100 c.c. of blood. The degree of cyanosis was not stated often enough to warrant any attempt to correlate it with spectroscopic values for sulfhemoglobin in the blood.

TABLE III. SYMPTOMS

SYMPTOMS		CASES	TOTAL
Headache			40
Functional (that is, tension or migraine)		31	
Hypertensive		6	
Malignant (group 4 hypertension)	2		
Possibly related to blood pressure; tension (?)	4		
Organic (presumably?)		3	
Due to carcinoma of nose and ethmoid sinuses	1		
Due to multiple sclerosis	1		
Due to carcinoma of lung, type of headache unknown	1		
"Nervousness," lift, and habit			3
Pain			12
Skeletal		5	
Abdominal		7	
Infection			2
Carbuncle of nose		1	
Of bladder		1	
Symptoms not stated			5
Hypertension		2	
Asthmatic bronchitis		1	
Subacute disseminating lupus erythematosus		1	
Periarteritis nodosa		1	

Determinations of the bromide present in the blood were made for the majority of patients who were taking Bromo-Seltzer. Levels were found to range from 8 to 204 mg. per 100 c.c. Patients who had high levels of bromide in the blood often complained of the outstanding symptoms of bromide intoxication, that is, bromide rash, slowed cerebration, ataxia, weakness, dysarthria, and mental confusion. Until the drug being ingested had been ascertained, this clinical picture was puzzling in a few cases, especially when cyanosis due to sulfhemoglobinemia was present also. Determinations of the values of sulfhemoglobin and bromide in blood were made on separate days in most cases in which the patients were taking Bromo-Seltzer. Consequently, any attempt to correlate the levels of bromide and sulfhemoglobin in the blood did not seem feasible. Likewise, there seemed to be poor correlation in most instances between the dose which the patients stated they were taking and the level of sulfhemoglobin in the blood.

Except for the cyanosis usually present and evidence of bromidism in those taking Bromo-Seltzer, it seemed impossible in most instances to relate any of the patient's symptoms to the medication. Some possible exceptions to this were as follows: in one case constipation ceased six days after ingestion of "B. C." (phenacetin, aspirin, and caffeine) tablets was discontinued. In another, chronic

headaches ceased after appendectomy when the patient discontinued ingestion of Bromo-Seltzer. In a third case constipation began after acetanilid was taken for pain. Another patient came to the clinic because of symptoms due to rather severe peripheral neuritis. It was the final opinion of the various neurological consultants who saw this last patient that the neuritis most likely was due to chronic acetanilid intoxication from ingestion of Bromo-Seltzer.

None of the patients had significant anemia, though in a few cases values of hemoglobin and, more rarely, the number of erythrocytes were reduced slightly. Monocytosis was noted on the blood smear of one patient. Gross,[7] in his comprehensive review, has noted that anemia, when present, is usually of slight or medium degree, though in some reported cases the number of erythrocytes was less than 2,000,000 per cubic millimeter. Agranulocytosis or significant neutropenia was not noted in any of our cases although it has been reported in a few cases after administration of acetanilid.[12,13]

In two cases the anticipated amount of functioning hemoglobin as determined indirectly from the spectroscopic determination of sulfhemoglobin was poorly correlated with the total quantity of hemoglobin and the amount of functioning hemoglobin as determined by means of oximeter readings and studies of respiratory function.

The concentration of hemoglobin of the patient who had 10 Gm. of sulfhemoglobin per 100 c.c. of blood was calculated to be 11.9 Gm. per 100 c.c. of blood from the spectrometric readings. This suggests that there were only 1.9 Gm. of functioning hemoglobin since sulfhemoglobin is presumably inert as far as oxygen-carrying capacity is concerned. Functional studies, however, gave values of approximately 10 Gm. of functioning hemoglobin per 100 c.c. of blood, that is, of hemoglobin capable of carrying oxygen, and between 3 and 6.5 Gm. of nonoxygen-carrying pigment per 100 c.c. of blood. These latter figures are more in accord with the clinical state of the patient who, despite a marked degree of cyanosis, had only minimal dyspnea on exertion. It is obvious from these figures that either sulfhemoglobin has some oxygen-carrying ability or that spectroscopic determinations of sulfhemoglobin are inaccurate. We believe the latter is the most likely explanation of this discrepancy.

The patient, a woman, 52 years old, came to the clinic because of severe headaches of the tension-migraine type which had been present for many years. She also had moderate hypertension but no evidence of cardiac, coronary, or renal insufficiency. She had been taking large amounts of phenacetin in a headache capsule. When she became blue, both she and the physician became alarmed about the possibility of her "heart failing." Despite the high level of su'fhemoglobin, the patient had been working regularly in an office. The associated complaints of chronic fatigue, nervousness, and constipation had been present for years prior to the onset of cyanosis, but had been somewhat worse during the preceding year, during which time she had been taking the present headache medicine.

COMMENT

In 1930, Harrop and Waterfield[8] reported ten cases of sulfhemoglobinemia. They stated that only thirty cases had been reported in the literature, and only five of these thirty were among patients who lived in this country. The simi-

larity between their findings and those of this study can be noted from the fact that in seven of their ten cases, Bromo-Seltzer was considered a causative agent; in seven of nine constipation was present; emotional instability was noted in nine cases. There was little if any respiratory distress in any case despite some rather severe degrees of cyanosis, and methemoglobinemia was not noted in any of their patients.

The remarkable similarity in the high incidence of use of acetanilid (either alone or combined with bromide, as in Bromo-Seltzer) in the two groups of patients is most surprising when the decreased use of acetanilid by physicians now as compared to 1930 is considered. This would suggest that, in most cases of sulfhemoglobinemia occurring at present, the acetanilid was not recommended by a physician.

While both methemoglobinemia and sulfhemoglobinemia have been reported[7,14] in the same case after administration of acetanilid, the failure of the former to occur in our series of patients suggests that it must be an infrequent occurrence. Furthermore, acetanilid was not the causative agent in any of the forty-nine cases of methemoglobinemia mentioned earlier in this report.

The high incidence of Bromo-Seltzer medication seems to us to warrant special comment. This proprietary remedy is widely advertised and available at the patient's request from most drug stores. It is reported to be effective in the relief of certain types of headaches, but unfortunately its use by the neurotic type of person who is especially likely to have recurrent headaches is often abused. While no serious harm seemed to have come to our patients (with the exception of the patient partially disabled by peripheral neuritis), they did in many instances get into some difficulty because of the large doses consumed. This was especially true regarding the bromide portion with its resultant signs of intoxication. Whether acetanilid actually does in some instances perpetuate and aggravate headache and constipation cannot be answered from this study. It is of interest that Harrop and Waterfield[8] attributed the emotional instability in their patients to the drug, but considered it possible that the headaches and constipation were contributing factors. It seems more likely that the continued ingestion and abuse of the drug, headaches, and associated nervous symptoms were all a part of the neurotic picture.

The occasional occurrence of sulfhemoglobinemia after ingestion of phenacetin is of interest since it is widely used in combination with aspirin and caffeine in the treatment of headache, that is, in Anacin, Stanback, Empirin and aspirin, phenacetin, and caffeine. It is obvious that sulfhemoglobin after ingestion of phenacetin is dependent on taking large amounts of the drug over extended periods of time, or sulfhemoglobinemia would be seen more frequently following its use. As quoted by Gross,[7] Snapper and later Harrop and Waterfield showed that both phenacetin and acetanilid caused sulfhemoglobinemia when given with sulfur to dogs. When phenacetin or acetanilid was given alone, methemoglobin resulted. Harrop and Waterfield theorized on the basis of this experiment that constipation was the added factor which gave rise to sulfur through production of an excess of hydrogen sulfide. While an intriguing idea, to our knowledge, it still lacks documentary

proof. Our study gave us no new information regarding this point. The fact that such a high percentage of our patients who had values of more than 2 Gm. of sulfhemoglobin per 100 c.c. of blood were constipated at least suggests that constipation does fit into the picture; just where, we cannot say at this time.

SUMMARY

The records of sixty-two patients with sulfhemoglobinemia encountered at the Mayo Clinic from May, 1939, to February, 1950, were reviewed, and the present knowledge regarding sulfhemoglobinemia and methemoglobinemia was presented. Bromo-Seltzer and acetanilid alone had been ingested by the majority of patients, with sulfonamide and phenacetin alone or in combination with other drugs by the remainder.

The medicaments had been used by the majority of patients for headache which was considered by us to be of neurotic origin.

A large percentage of patients who had a concentration of 2 Gm. or more of sulfhemoglobin per 100 c.c. of blood were constipated. Constipation was an infrequent complaint of the remainder (the majority), who had less than 2 Gm. of sulfhemoglobin per 100 c.c. of blood.

Evidence of bromide intoxication and high levels of bromide in the blood were occasionally seen in patients taking Bromo-Seltzer.

Despite a severe degree of cyanosis and very high levels of sulfhemoglobin in the blood of two patients, there was little or no evidence of respiratory distress, and studies of respiratory function showed higher levels of functioning hemoglobin than might be inferred from the total hemoglobin and sulfhemoglobin levels as determined spectroscopically. Our study indicates, too, that sulfhemoglobinemia is more common than methemoglobinemia.

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THE EFFECTS OF CIGARETTE SMOKING ON THE BALLISTOCARDIOGRAM

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A YOUNG man engaged in ballistocardiographic research discovered that on some occasions his own tracings were normal, on others remarkably abnormal. Although he never had had any discomfort from smoking, it became apparent that this was the cause of the change, and a systematic study of a group of young smokers and of patients with Buerger's disease was undertaken.

METHOD

All subjects used in the test refrained from smoking for a period of not less than 2 hours. Simultaneous electrocardiogram (one lead), capillary finger pulse,[1] and electromagnetic ballistocardiogram[2] were recorded. Control tracings were taken during normal breathing, held inspiration, held expiration, and following a few minutes of deep breathing. With the subject in the same position, he was given a standard brand cigarette to smoke. Repeat multiple simultaneous tracings were taken after the cigarette was smoked by the subject in his usual manner and again at varying intervals thereafter. No records were taken more than 20 minutes after the cigarette was finished.

A group of 31 individuals was studied. Of these, 23 were normal, healthy persons with no evidence of vascular or other disease. Of the remainder there were 3 with coronary artery disease, one with arteriosclerotic peripheral vascular disease, 3 with Buerger's disease, and one with rheumatic heart disease and pleural effusion. Two of the normal subjects were nonsmokers.

RESULTS

Of the 31 subjects tested, 18 showed some changes in their ballistocardiogram as a result of smoking one standard brand cigarette. Seven of the 18 could be classified as having shown great changes and the remaining 11 as having shown minor changes. The minor changes were primarily increases in respiratory variation with no distortion of the waves (Fig. 1). Also included in this minor group were those who showed a decrease in the amplitude of the waves with only slight respiratory variation and no distortion of the ballistocardiographic complexes. The severe changes were marked respiratory variations and, in addition,

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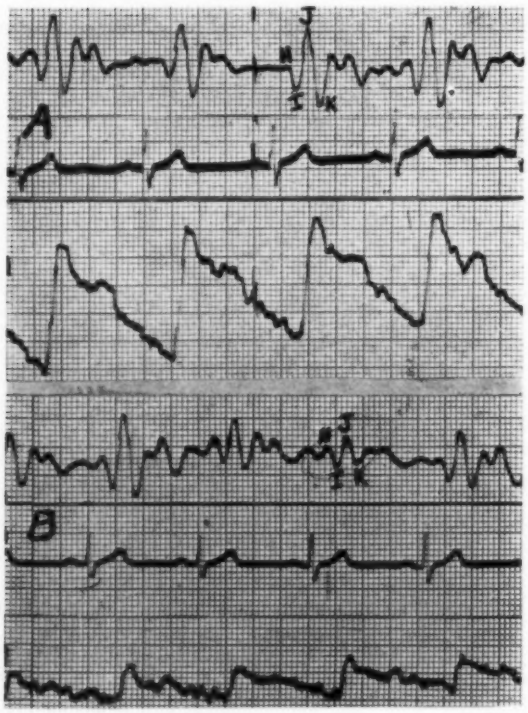

Fig. 1.—The effect of smoking on a healthy man, 22 years old. *A*, Simultaneous longitudinal ballistocardiogram, electrocardiogram, and finger pulse taken prior to smoking; *B*, immediately after patient smoked. Note the increase in respiratory variation and the decrease in amplitude of the digital pulse after smoking.

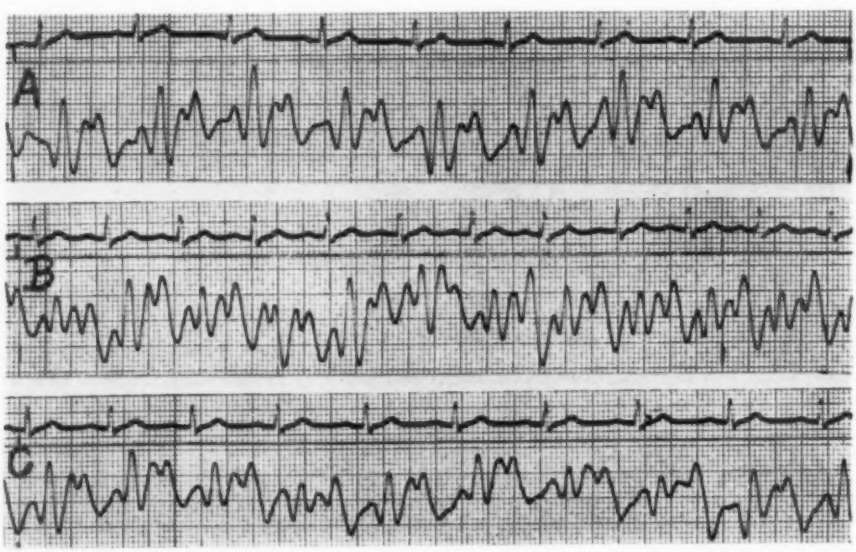

Fig. 2.—The effect of smoking on a healthy man, 30 years old. *A*, Control; *B*, end of cigarette. Note the small J and large N-O stroke in expiration. In the last 5 cycles N-O would be mistaken for J-K without the synchronous electrocardiogram. *C*, six minutes after cigarette, recovery is incomplete (same features as in *B*).

some distortion of the ballistocardiographic complexes (Figs. 2, 3, 4, and 5). In an occasional case a hyperkinetic response, as evidenced by an increase in amplitude of the waves, was noted. Of the 7 subjects classified as having shown severe changes, 4 were normal young adults, 2 had Buerger's disease, and one had had a myocardial infarct 8 months previously.

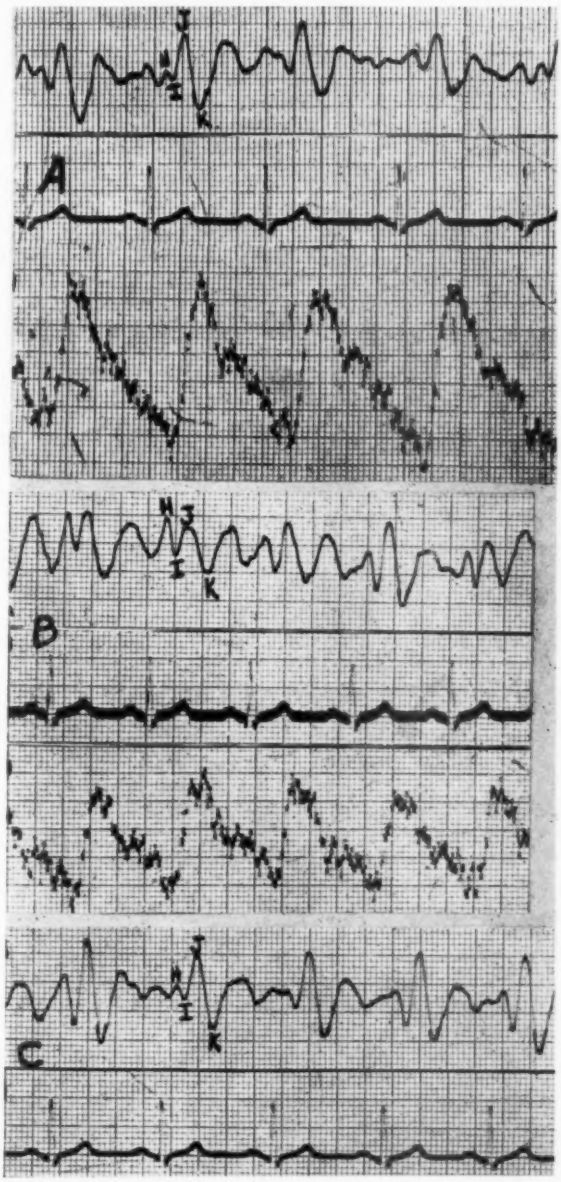

Fig. 3.—The effect of smoking on a healthy man, 28 years old. *A*, Control; *B*, immediately after smoking. Note the distortion of the ballistocardiographic complexes and the marked increase in the height of the H wave. *C*, Record taken one minute after the subject had finished the cigarette. The ballistocardiographic complexes have returned to normal.

It was of interest that the most marked change of all the ballistocardiographic records taken was noted in a subject with Buerger's disease (Fig. 4). Two of the 3 with Buerger's disease recorded had severe changes; the third also showed an increase in respiratory variation as a result of smoking, but evaluating the degree of change in the complexes was unsatisfactory since the subject had had an abnormal ballistocardiogram prior to the test.

Most subjects who showed a change in the ballistocardiogram as a result of smoking reverted to normal within 10 minutes. One subject (Fig. 3) reverted to normal in less than one minute.

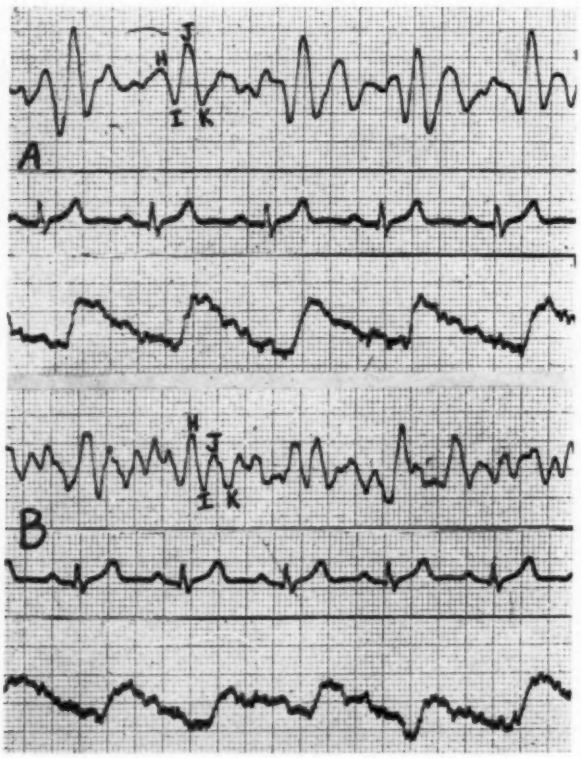

Fig. 4.—The effect of smoking on a 46-year-old man with Buerger's disease. *A*, Control; *B*, immediately after patient smoked. Note the distortion of the ballistocardiographic complexes and the increase in the height of the H wave.

The electrocardiogram which was recorded as a timer for the ballistocardiogram was also analyzed. The need for a timer can be seen in Fig. 2. Only 4 of the 31 subjects tested demonstrated some change in the electrocardiogram as a result of smoking. The changes consisted of a decrease in amplitude of the T waves and the QRS complex. Graybiel and associates[3] reported electrocardiographic changes in 20 out of 45 subjects tested. Evans and Stewart[4] reported that 71 per cent showed changes in the electrocardiogram after smoking. It should be emphasized that we recorded only one lead of the electrocardiogram, whereas the other investigators recorded multiple leads. It was interesting to

note that the 4 subjects who had changes in the electrocardiogram as a result of smoking were in the group that had changes in the ballistocardiogram; 2 were in the group that showed marked changes, and the other 2 were in the mild group.

The photoelectric capillary finger pulse, as expected, showed a marked decrease in the amplitude of the wave as a result of cigarette smoking. This decrease in peripheral blood flow was found in all subjects. No attempt was made to quantitate the decrease of the capillary pulse, and from inspection it would not be possible to say that greater vasoconstriction was observed in the group with maximal changes in the ballistocardiogram.

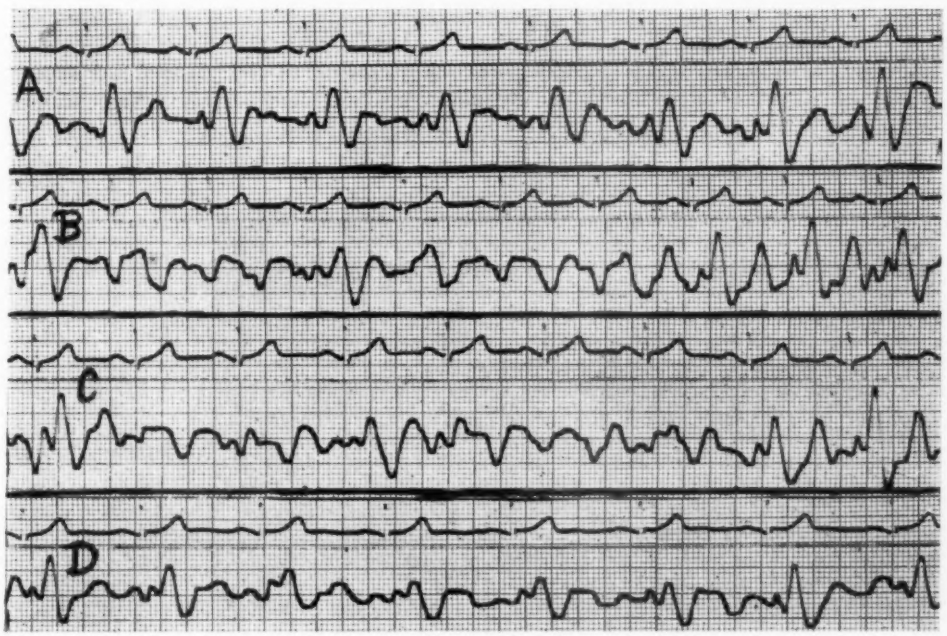

Fig. 5.—The effect of smoking on a 41-year-old man, 8 months after recovery from myocardial infarction. *A*, Control; *B*, one-fourth of a cigarette has been smoked; *C*, cigarette finished; *D*, 20 minutes later, recovery incomplete.

In an attempt to ascertain the effects of the pure nicotine alkaloid on the ballistocardiogram, a drop of the dissolved alkaloid was placed on the tongue of one of the nonsmoking normal subjects after a control tracing had been taken. Fig. 6 shows the remarkable and severe changes resulting from the absorption of nicotine. It was felt that a considerable amount of the alkaloid had been absorbed as evidenced by the patient exhibiting a severe reaction consisting of a burning sensation in the mouth, transient nausea, vomiting, generalized weakness, and some mental confusion. The marked changes noted in the ballistocardiogram as a result of the pure nicotine were complete loss of the previously normal pattern and the presence of notched J waves, and the largest wave in most complexes was seen to occur in diastole.

To simulate the severe bitter taste of nicotine upon the tongue, a substance (Decholin) having no known untoward pharmacological effects was likewise

tested. The changes in the ballistocardiogram that resulted were primarily associated with an increase in salivation, swallowing, and hyperventilation and in no way comparable to those produced by nicotine.

DISCUSSION

The exact mechanism whereby cigarette smoking can result in an increase in respiratory variation or a distortion of ballistocardiographic complexes is not clear at this time. The changes in electrocardiograms do not suggest that it is due to coronary vasoconstriction. An effect on the vigor of systolic contraction is suggested since the changes in the ballistocardiogram resemble those frequently seen after myocardial infarction. De Lalla and Brown[5] believe that an increase in respiratory variation may be due largely to diminution of the volume of blood in the pulmonary pool. Perhaps cigarette smoking may lead to peripheral pooling chiefly in the portal area or may alter respiration and thereby cause a diminution of the pulmonary pool.

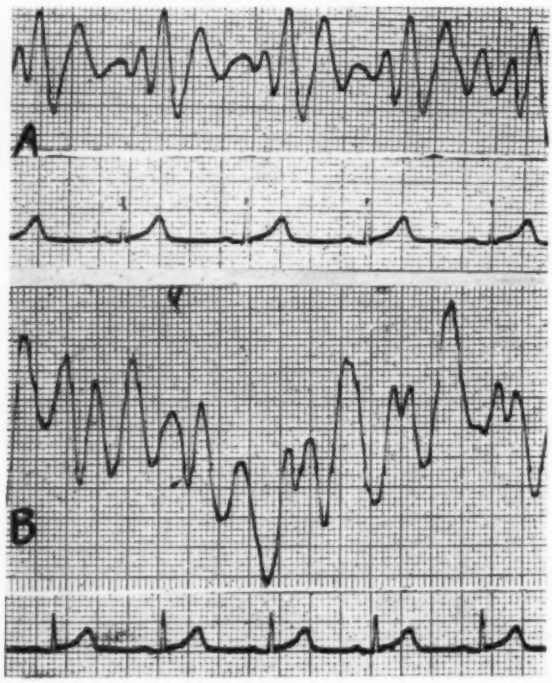

Fig. 6.—The effect of placing pure nicotine on the tongue of a 24-year-old healthy nonsmoker. *A*, Control; *B*, immediately after nicotine was placed on tongue. Comment in text.

Perhaps the changes seen are due chiefly to an increase in sympathetic tone and peripheral vasoconstriction, even though blood pressure rises are not comparable to the changes in the ballistocardiographic pattern.

In fact, confusion exists as to the explanation of the standard vascular changes (decreased peripheral blood flow, increased blood pressure, increased pulse, and electrocardiographic changes) commonly seen after smoking a cigar-

ette. Maddock and Coller,[6] injecting 1 mg. of nicotine intravenously, reported that they could reproduce the vascular changes that are brought about by smoking. They also reported that negligible changes resulted from smoking cubeb cigarettes (without nicotine). Evans and Stewart[4] reported that the vascular changes resulting from the smoking of a standard brand cigarette could also be obtained if a denicotinized cigarette was used. It is their belief that the sympathetic stimulation brought about by the irritating effect of smoking upon the respiratory tract, independent of nicotine, may be responsible for the observed changes.

Mulinos and Shulman[7] reported a decrease in peripheral blood flow as a result of deep breathing. In our records we occasionally noted that tracings taken after deep breathing showed an increase in respiratory variation and a decrease in capillary pulse. However, these changes were not present in all subjects who showed changes as a result of smoking and when present were never as marked. It is difficult to attribute the effects of smoking to deep breathing alone, for deep breathing in no way simulates the effect of smoking. Moyer and Maddock[8] reported that respiratory movements imitating actual smoking as nearly as possible had negligible changes on the pulse, blood pressure, and cutaneous temperature. This is in accordance with one of our cases where smoking a cigarette caused a severe change in the ballistocardiogram, but sham smoking caused no change.

As is well known, the effects of a first cigarette or even the first one in the morning for some habitual smokers are more striking than those which follow. Marked changes, such as occurred in 7 of 31 subjects, probably are evidence of inability to develop tolerance with habituation rather than of sensitivity, judging by the effect of nicotine on a nonsmoking subject.

SUMMARY

1. Of 31 tested subjects 18 showed changes in the ballistocardiogram as a result of smoking one standard cigarette. All subjects showed a decrease in amplitude of the digital pulse.

2. Eleven of the 18 had minor changes which consisted primarily of an increase in respiratory variation.

3. Seven had severe changes which consisted of an increase in respiratory variation and distortion of the pattern of the curve. These were transient, disappearing in one to twenty minutes.

4. Deep breathing affects the ballistocardiogram and the pulse in the finger tips, but in no way approaches the effects of smoking.

5. Nicotine alkaloid placed on a subject's tongue produced drastic changes in the ballistocardiogram along with the symptoms of mild nicotine poisoning familiar to nonsmokers taking their first cigar.

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PROCAINE AMIDE COMPARED WITH QUINIDINE AS A THERAPY FOR ARRHYTHMIAS

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IN A previous report[1] it was shown that procaine amide is clinically effective in the treatment of auricular arrhythmias. The present report attempts to answer two questions:

1. What is the clinical value of procaine amide in the treatment of arrhythmias? Until now quinidine has been the drug of choice. How does procaine amide compare with it clinically?

2. Does procaine amide have a preferential effect on ventricular arrhythmias as compared to auricular? This has been inferred by those[2] who claim that it is clinically effective only in patients with ventricular and not in patients with auricular arrhythmias. This study attempts to ascertain any preferential effect. This can be done by comparing it quantitatively with quinidine in both types of cases. It is reasonable to assume that quinidine acts equally well on both types of arrhythmias. If procaine amide is more effective in the ventricular variety, then the ratio, effective dose of procaine amide/ effective dose of quinidine, should be smaller in a case of ventricular extrasystoles or tachycardia than in a case of auricular extrasystoles or fibrillation. If there is no preferential action, then the ratio should be the same for both types of cases.

The effect of different doses of the two drugs was measured in two patients with a ventricular arrhythmia and in one patient with an auricular arrhythmia. The above ratio was estimated for each case. The results fail to show any preferential effectiveness on the ventricular variety.

METHOD

By administering both drugs singly or combined to the same patient and observing the effects of various dosages, it is possible to evaluate their relative effectiveness. Suitable patients for such a comparative evaluation are rare. The subject must have a chronic or recurrent arrhythmia so that many trials may be made to permit a reliable determination of the average effect. The sensitiveness to the drugs and the intensity of the arrhythmia should not vary. The response must be measurable, preferably in an objective manner. However, a subjective response can also be satisfactory, as in Case 1, if the patient is intelligent, cooperative, and aware of the arrhythmia.

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Lewis and associates[3] described a method for comparing the antiarrhythmic activity of drugs in patients with chronic auricular fibrillation. By the use of special chest leads they registered the F waves in such a manner that the rate could be estimated. This varied with the dose and effectiveness of the drug.

Otto and Gold[4] described a method for estimating the frequency of extrasystoles. The ability of a given drug in a given dose to suppress them was a measure of the drug's potency. Similar methods were employed in this study. Details of the case, the method, and the results are so intimately related with one another that each case is discussed separately.

The drugs used were procaine amide hydrochloride* in capsules, each containing 0.25 Gm., and quinidine sulfate as capsules or tablets, each containing 3 gr. (0.20 Gm.). Only oral medication was used. No attempt was made to compare the drugs by the intravenous route.

CLINICAL OBSERVATIONS

CASE 1.—T. H. was a 40-year-old white man with aortic insufficiency of rheumatic origin. For the past five years, at intervals of three to four weeks, he had experienced attacks of ventricular tachycardia lasting three to five days. Between attacks he was conscious of frequent and annoying extrasystoles which were shown to be ventricular in type in the electrocardiogram. It was found that the minimum daily dose of quinidine to keep him free from annoying arrhythmias was 18 gr. divided into three doses. On this dosage he noticed only occasional extrasystoles, and, at about the time of the expected prolonged attack, he experienced instead rare spells of tachycardia lasting only a moment or two.

TABLE I. CASE 1. EFFECTS OF DIFFERENT DOSES AND COMBINATIONS OF PROCAINE AMIDE AND QUINIDINE ON THE INCIDENCE OF VENTRICULAR EXTRASYSTOLES AND TACHYCARDIA

EXPERIMENT NO.	DAILY DOSE			DURATION OF TRIAL	EFFECT
	QUINIDINE SULFATE GRAINS (0.065 GM.)	PROCAINE AMIDE CAPSULES (0.25 GM.)	TOTAL UNITS†		
1	18	0	18	3 weeks	Occasional extrasystoles
2	15	2	17	3 days	Increased number of extrasystoles
3	18	2	20	3 days	Occasional extrasystoles
4	6	8	14	2 weeks	Several short attacks of tachycardia; many extrasystoles
5	6	10	16	5 days	One short attack of tachycardia; frequent extrasystoles
6	6	12	18	1 week	Occasional extrasystoles
7	3	15	18	5 days	Increased number of extrasystoles
8	3	17	20	1 week	Rare extrasystoles
9	0	20	20	1 week	Occasional extrasystoles
10	0	23	23	1 week	Rare extrasystoles
11	12	8	20	1 week	Rare extrasystoles
12	18	0	18	1 week	Occasional extrasystoles
13	15	0	15	3 days	Increased number of extrasystoles
14	18	0	18	12 weeks	Occasional extrasystoles

†A unit represents either 1 gr. (0.065 Gm.) of quinidine sulfate or 1 capsule (0.25 Gm.) of procaine amide hydrochloride.

*Pronestyl, a brand of procaine amide, was supplied by E. R. Squibb & Sons, New York, N. Y.

He was always aware of the occurrence of extrasystoles or tachycardia. Since he was intelligent and cooperative, it was possible to use his subjective response for estimating the ability of a drug to suppress the arrhythmia.

The daily dose of procaine amide, quinidine, or both was divided into three more or less equal parts. The dosages, the various combinations, and the results are shown in Table I and Fig. 1.

One notes that 18 capsules (4.5 Gm.) of procaine amide had approximately the same effect as 18 gr. (1.2 Gm.) of quinidine. Any combination of grains of quinidine or capsules of procaine amide that added up to 18 or more was satisfactory. These findings indicate that 1 capsule (0.25 Gm.) of procaine amide had approximately the same effectiveness as 1 gr. (0.065 Gm.) of quinidine. When both were given together in various proportions, the results showed only additive effects. There appeared to be neither potentiation nor antagonism.

The patient preferred quinidine to procaine amide because of the lesser number of capsules in the daily quinidine dose. When he took 20 capsules of procaine amide daily, he felt slightly nauseated.

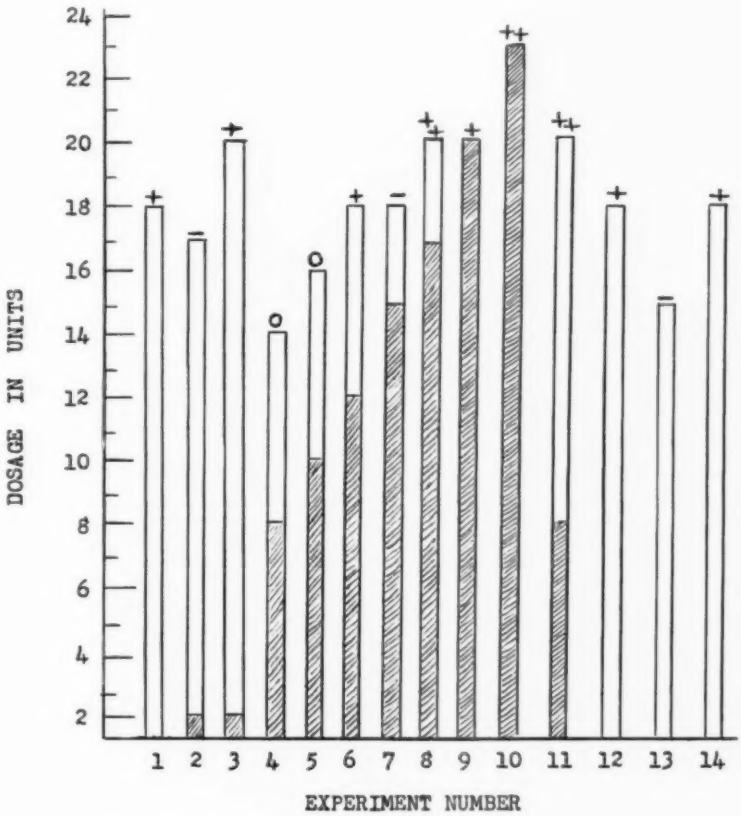

Fig. 1 (Case 1).—Bar graph showing the effect of different oral doses and combinations of procaine amide and quinidine on the incidence of ventricular extrasystoles and tachycardia. The height of each bar represents the total daily dose. The length of the clear area of the bar indicates the daily dose of quinidine in grains, and the length of the hatched portion of the bar indicates the daily dose of procaine amide in capsules of 0.25 Gm. each. A unit of dosage is equal to 1 gr. (0.065 Gm.) of quinidine or 1 capsule (0.25 Gm.) of procaine amide. The number under each bar corresponds to the experiment number indicated in Table I.

The symbols above the bars indicate the result of the dosage on the arrhythmia. 0 signifies many extrasystoles and short attacks of tachycardia. — indicates an increase in the number of extrasystoles. + indicates a satisfactory condition with only occasional extrasystoles. ++ indicates a very satisfactory condition with rare extrasystoles.

In the four months since the conclusion of the experiment, the patient has several times attempted to reduce the maintenance dose of quinidine below 18 gr. daily. This has always resulted in a disturbing increase in the incidence of extrasystoles and in the appearance of short attacks of tachycardia. This attests to the stability of the intensity of the arrhythmia.

CASE 2.—J. D. was a 39-year-old Negro man who suffered from aortic and mitral valvular disease of rheumatic origin. He was in chronic congestive failure and received a daily dose of digitalis and frequent injections of mercurials. The electrocardiogram showed a chronic coarse auricular fibrillation. The rate of F waves in V_1 could be measured with a fair degree of accuracy. In any one strip the F waves had varying rates. These were measured as F-F intervals and then averaged to give the dominant F-F interval. The control tracing taken before each test showed a constant average F-F interval of 0.13 second.

The tests took place in the morning about one hour after breakfast. First, a strip of 30 to 40 seconds was recorded of Lead V_1. Then the drug was given orally, and a similar tracing was recorded every hour for two to four hours. The average F-F interval was measured in each strip. The maximum average F-F interval was usually found in the two- or three-hour strip. This figure was used as a measure of the drug's action. The details of the dosages and the results are shown in Table II and Fig. 2.

TABLE II. CASE 2. THE MAXIMUM AVERAGE F-F INTERVAL FOLLOWING A SINGLE ORAL DOSE OF PROCAINE AMIDE OR QUINIDINE

EXPERIMENT NO.	DOSE		F-F INTERVAL*	TIME OF MAXIMUM EFFECT (HOURS)
	QUINIDINE SULFATE GRAINS (0.055 GM.)	PROCAINE AMIDE CAPSULES (0.25 GM.)		
1	6		15	2
2	3		16	2
3	9		18	2
4	12		21	3
5	18		24	2
6		9	20	3
7		12	23	3
8		6	18	2
9	6		17	3
10	9		19	2
11		9	17	2
12		9	19	2
13	9		19	2
14	12		21	2
15		12	23	2
16	12		20	2
17	15		22	2
18		6	19	2
19	6		17	3
20		6	19	3
21		12	22	2

*Before each experiment a control tracing was recorded. It always showed an F-F interval of 0.13 second.

The effect of 6 capsules (1.5 Gm.) of procaine amide was approximately equal to 9 gr. (0.6 Gm.) of quinidine; the effect of 9 capsules (2.25 Gm.) of procaine amide was approximately equal to 12 gr. (0.8 Gm.) of quinidine; and the effect of 12 capsules (3.0 Gm.) approximately equaled 15 gr. (1.0 Gm.) of quinidine. The respective ratios are 2.5 to 1, 2.8 to 1, and 3 to 1.

Nausea always occurred after taking 9 or more capsules of procaine amide. No side effects were noted following any dose of quinidine.

CASE 3.—M. M., a 43-year-old Negro man, was recovering from an acute cardiopulmonary illness of undetermined nature. Auscultation and electrocardiograms showed at all times frequent ventricular extrasystoles. There were frequent runs of bigeminy. The extrasystoles persisted undiminished throughout the entire hospital stay of six weeks, except when the patient was being treated with quinidine or procaine amide.

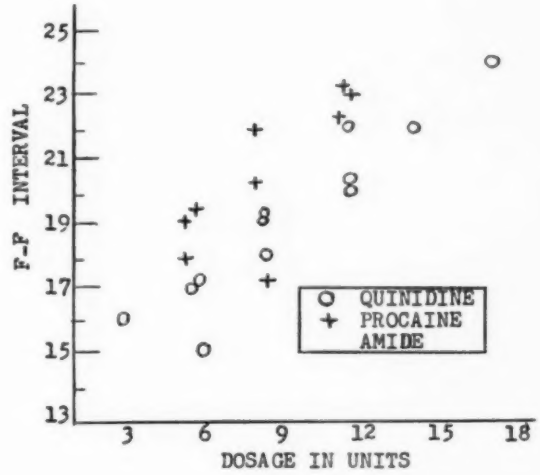

Fig. 2 (Case 2). —This shows the correlation between the size of a single oral dose of either drug and the resulting maximum average F-F interval. A unit of dosage is 1 gr. (0.065 Gm.) of quinidine or 1 capsule (0.25 Gm.) of procaine amide.

One set of comparisons was carried out with daily doses of the drugs as shown in Table III, experiments 1, 2, and 3. The daily dose was given in four equal parts. The results were noted by frequent auscultation and electrocardiograms. In another test the effectiveness of the two drugs was compared after a single dose. This is detailed in Table III, experiments 4 and 5. Between experiments 2, 3, 4, and 5 there was always an interval of at least forty-eight hours to insure the complete elimination of the previous test dose.

Experiments 1 and 2 showed that while 12 capsules (3.0 Gm.) a day of procaine amide were insufficient to suppress the extrasystoles, 24 capsules (6.0 Gm.) a day were enough. Experiment 3 showed that 24 gr. (1.6 Gm.) of quinidine also sufficed. This approximates a 4 to 1 ratio. Experiment 4 showed that 10 capsules (2.5 Gm.) of procaine amide in a single dose were able to diminish the frequency of the extrasystoles. Experiment 5 showed that 12 gr. (0.8 Gm.) had more effect in that it suppressed the extrasystoles completely for several hours. This indicates that 0.8 Gm. of quinidine was more potent than three times as much procaine amide. This agrees well with a 4 to 1 ratio.

The number of trials in this case was too few to establish an independent ratio of effectiveness for quinidine and procaine amide. However, the results do tend to confirm the findings of the first two cases.

DISCUSSION

The results indicate that the antiarrhythmic activity of procaine amide is about one-third to one-fourth that of quinidine. This applies to oral doses only.

One capsule (0.25 Gm.) of procaine amide is equal approximately to 1 gr. (0.065 Gm.) of quinidine. This corresponds to the findings of Newman and Clark[5] who reported that in tests on the refractory period of excised auricular muscle quinidine appeared to be four times as strong as procaine amide when measured by concentration of solution.

The absorption of procaine amide appears to be of the same rate as quinidine if one can judge by the time of the appearance of the maximum effect, namely, two to three hours.

TABLE III. CASE 3. THE EFFECTS OF DIFFERENT DOSES OF THE TWO DRUGS ON FREQUENT VENTRICULAR EXTRASYSTOLES

EXPERIMENT NO.	DOSE		DURATION OF TRIAL	EFFECT
	QUINIDINE SULFATE GRAINS (0.055 GM.)	PROCAINE AMIDE CAPSULES (0.25 GM.)		
1		8 to 12 daily	7 days	No definite diminution of extrasystoles
2		24 daily	2 days	Complete suppression of extrasystoles
3	24 daily		2 days	Complete suppression of extrasystoles
4		10	Single dose	Incidence of extrasystoles diminished
5	12		Single dose	Complete suppression of extrasystoles for several hours

No evidence was found for any preferential action on ventricular as compared to auricular arrhythmias. On the contrary, if the results are considered to be quantitatively exact, then a preferential action on auricular arrhythmia is indicated. Since the cases tested were few and the variables many in such human experiments, it is better to treat the results only as rough approximations. Both this and a previous investigation[1] indicate that procaine amide has an equal effect on both types of arrhythmias.

The two drugs were compared only for their antiarrhythmic ability. Fundamentally, this is the ability to suppress ectopic stimulus formation, for such is the basic mechanism of extrasystoles, paroxysmal tachycardia, flutter, and fibrillation.[6] No comparisons were made of the other cardiac effects which procaine amide shares in common with quinidine. These include prolongation of the QRS complex, prolongation of the Q-T interval, T-wave changes, a tendency to induce extrasystoles, and a tendency to increase the ventricular rate in cases of flutter and fibrillation by blocking the vagus. Nor was a comparison made on the tendency to depress the blood pressure and the contractility of the myocardium.

One of the limiting factors of quinidine therapy has been the occurrence of cinchonism as the dose is increased to 20 to 30 gr. (1.3 to 2.0 Gm.) daily. The symptoms are headache, tinnitus, and disturbed vision; even deafness and blindness may follow. Such symptoms are not known to follow procaine amide therapy. This may be due to an essential difference between the two drugs and would then be clinically a distinct advantage for procaine amide. More likely, it is due

to the difficulty of giving enough of the procaine amide in any one day to equal the effect of 30 gr. (2.0 Gm.) of quinidine. Such a dose involves 30 capsules. In the majority of patients this would cause nausea and vomiting.

It is not unusual to find a patient who is sensitive to quinidine and who develops fever, a skin eruption, or a purpura following even small doses. Such reactions have as yet not been seen following procaine amide, although the new drug has not been used widely enough to permit any evaluation of its propensity to cause unfortunate reactions.

The value of procaine amide in clinical practice may be defined as follows. It is approximately one-fourth as strong as quinidine. Therefore, for every 0.065 Gm. of quinidine needed for a given therapeutic effect, one can substitute 0.25 Gm. of procaine amide. This applies both to its desirable antiarrhythmic qualities as well as to the other less desirable cardiac and extracardiac effects. Therefore, the same indications and contraindications which have been known to apply to quinidine therapy should also hold true for treatment with procaine amide.

Effective dosage of procaine amide frequently requires the ingestion of uncomfortably large numbers of capsules; this has a definite disadvantage. It causes more nausea and vomiting than quinidine for the same effective doses. The oral use of procaine amide appears to be limited to those patients in whom quinidine causes skin eruptions, blood dyscrasia, fever, and so forth. When the limiting factor is an undesirable cardiac action such as excessive widening of the QRS complex or suppression of the sinoauricular pacemaker, then there is no reason to expect better toleration from procaine amide. Further experience may show that this statement is too rigid. Cases may be found in which the cardiac action of procaine amide has a different and more advantageous spectrum than quinidine.

When an arrhythmia has to be treated by the intravenous route, then procaine amide appears to be superior to quinidine. It is available in a stable solution already prepared, and it does not cause any discomfort if it is injected outside the vein. While recognizing these matters as having considerable clinical importance, one must never overlook the dangers inherent in the administration of a quinidine-like substance intravenously. To make an intravenous administration safe, it is necessary to inject slowly, preferably by drip, to take the blood pressure every minute, and to take a direct-writing electrocardiogram during the injection.

Should the need for intramuscular therapy arise, it is probable that procaine amide will be useful, though the large bulk (10 c.c.) for every gram would be a disadvantage.

CONCLUSIONS

1. A quantitative comparison of the antiarrhythmic potency of procaine amide and quinidine was made in two patients with ventricular and one patient with auricular arrhythmias.

2. The results indicate that quinidine is approximately four times as strong as procaine amide on a weight basis. For every 0.065 Gm. of quinidine needed for a given therapeutic effect, one can substitute approximately 0.25 Gm. of procaine amide.

3. The results indicate that procaine amide does not have a preferential effectiveness on ventricular as compared to auricular arrhythmias.

4. The oral use of procaine amide is seriously limited by its tendency to cause nausea and vomiting and by the large number of capsules required for an average effective dose.

5. Procaine amide can be a satisfactory substitute in those patients who are sensitive to quinidine.

6. When intravenous therapy is indicated, procaine amide appears to be superior to quinidine.

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THE EFFECTS OF TUBING BORE ON STETHOSCOPE EFFICIENCY

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IN A previous communication,[1] we stated that stethoscope performance is dependent upon the length and caliber of the rubber tubing. Measurements were made to ascertain the actual change in efficiency of a binaural system by altering the length of the rubber tubing. Our data showed that below about 100 cycles per second, the efficiency is not affected materially by tubing length. From about 100 cycles per second to 1,000 cycles per second, tubing length exhibits a considerable effect upon stethoscope efficiency; that is, the efficiency decreases with increased tubing length. We concluded that the changes in the efficiency of an acoustic stethoscope which are caused by varying the length of the tubing, although not given any consideration by stethoscope users, produce an effect upon the quality of the heart sounds and the ability to hear low-intensity murmurs of medium and high frequency. For example, at 200 cycles per second there is a 15 decibel attenuation of the sounds when two rubber tubes, each 26 inches long (commercial stethoscope tubing, with a caliber of 3/16 inch), are substituted for two similar tubes 3 inches in length. The sound is about eight times as loud in the short tubing system. This attenuation occurs in the region where the low-intensity, high-pitched basal diastolic murmurs are present, and every possible increase in efficiency in this region is of utmost value.

Our analysis also indicated that the auscultatory sound pressure variations at the ear, produced by the motion of the skin or Bakelite diaphragm, are inversely proportional to the internal volume of the stethoscope, so that an infinitely small volume would theoretically exhibit a maximum variation in pressure, which, in turn, would manifest itself as a sound of maximum intensity. The skin diaphragm effect is produced when the open bell chest piece is placed on the surface of the chest, and the Bakelite diaphragm effect is produced by means of the Bowles chest piece. Obviously, therefore, the tubing, according to this form of reasoning, should be as short as possible and the caliber as small as possible. Also, the wall of the tubing should be sufficiently rigid for maximum efficiency, for any wall motion reduces the effective pressure variation transmitted to the observer's ear.

We also indicated that a factor that must be taken into consideration is the frictional resistance offered to the air column by the walls of the rubber tubing. That is, the efficiency of a stethoscope decreases as the resistance to the pressure variations is increased; the resistance is increased as the caliber is decreased. In eliminating the resistance component, we have still to consider that the greater the volume, the less the efficiency. Therefore, to obtain the most efficient tubing

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for a stethoscope, one should make the tubing as short as possible and compromise on the resistance components. Due to the lack of suitable instrumentation at the time these experiments were performed (1939 to 1941), exact determinations were not made with regard to tubing bore.

During World War II, a sound pressure meter[2] was devised by the Research on Sound Control group at Cruft Laboratory, Harvard University. One of us (M.B.R.) collaborated on the project in putting this instrument in a practical and reproducible form. With the aid of this sound pressure meter and several other devices, we were enabled to make finite measurements pertaining to stethoscope tubing caliber.

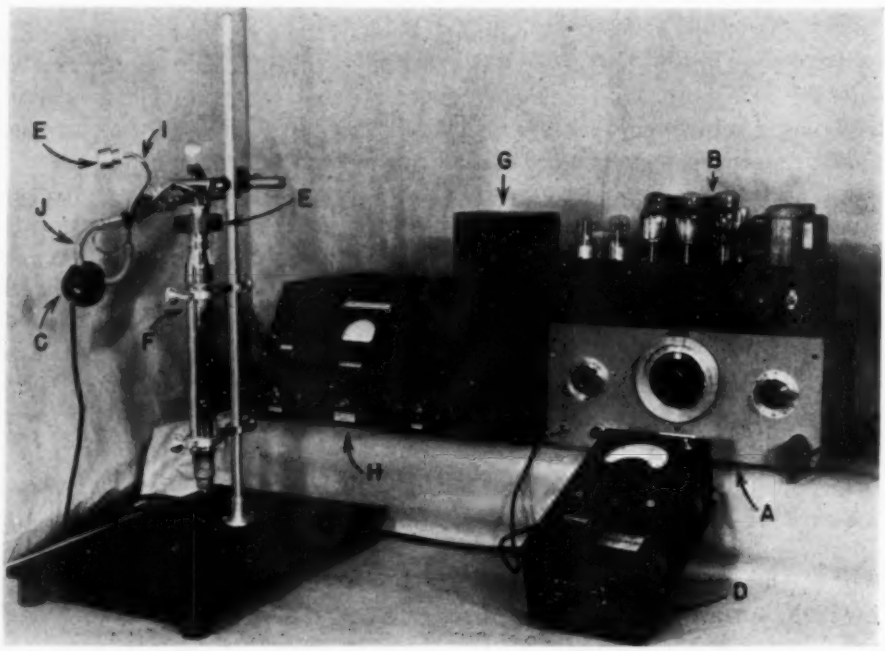

Fig. 1.—Instrumentation for determining the effects of tubing caliber on acoustical stethoscope efficiency. The components are: *A*, adjustable frequency oscillator; *B*, amplifier; *C*, calibrated audiophone; *D*, vacuum tube voltmeter; *E*, artificial ears; *F*, sound pressure meter; *G*, decade box; *H*, sound pressure meter control box; *I*, binaurals; *J*, stethoscope tubing.

METHOD

Fig. 1 is a photograph of the instrumentation used for the determination of the effects of tubing caliber on acoustical stethoscope efficiency. Basically, a sound pressure meter is an instrument or combination of instruments comprising a microphone, amplifier, and indicating meter with a flat or uniform response as a function of frequency in the desired frequency spectrum. It indicates the value of the sound pressure in dynes per square centimeter or decibels above a reference, such as the average human threshold of hearing. The commonly used threshold reference is equal to 0.000200 dynes per square centimeter.

When making a sound pressure determination, the adjustable frequency oscillator, *A*, is set at a predetermined frequency (Fig. 1). By means of the oscillator intensity control and the amplifier, *B*, just above it, a sinusoidal electrical signal is applied to the calibrated audiophone, *C*.[1] The intensity of the electrical signal which enters the audiophone is monitored by means of the vacuum tube voltmeter, *D*. The audiophone transforms the electrical signal into an equivalent sound which is conducted by the stethoscope tubing to the artificial ears, *E*. An artificial ear[3] is an acoustical cavity whose acoustical impedance is intended to simulate the impedance of the average human ear. In Fig. 2 may be seen a close-up view of the artificial ears used in this investigation. The spirallike tube visible on the artificial ear to the right is a high pass filter which

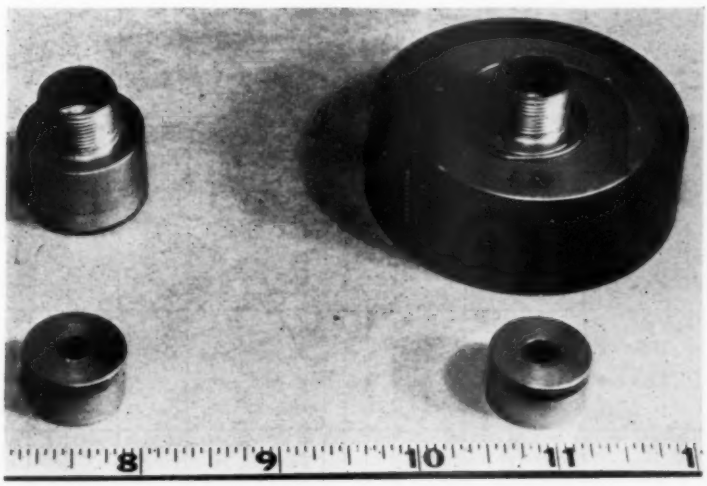

Fig. 2.—Artificial ears which simulate the acoustical impedance of the average human ear.

simulates the action of the Eustachian tube and prevents a build-up of constant pressures on the sound pressure meter, *F*, shown in Fig. 1. The sound pressure meter in turn measures the pressure of the sound at the ear pieces of the binaurals in dynes per square centimeter or decibels above threshold. The decade box, *G*, between the oscillator and sound pressure control box, *H*, is for the purpose of electrical impedance matching so that constant power at varying frequencies is delivered by the audiophone to the tubing.

The binaurals used in this investigation were of the common commercial design with a length of 9 inches for each ear and a bore diameter of 3/16 inch. An arbitrary tubing length, *J*, of 26 inches was selected, and frequency response curves were obtained. Essentially, the tubing length in this investigation is discounted because a comparison is made between the efficiencies of tubes of equal length but varying caliber.

RESULTS

Fig. 3 shows the response curves of tubing whose caliber varies between 1/4 and 3/64 inch. The axis of abscissas of the graph is expressed in frequency or

cycles per second of the applied signal, and the axis of ordinates is expressed both in dynes per square centimeter and in the equivalent number of decibels above the threshold reference of 0.0002 dynes per square centimeter.

The family of curves shows:

1. From about 115 cycles per second down to 40 cycles per second, the tubing with a 1/8 inch bore is the most efficient.
2. Tubing with a 3/64 inch bore is most efficient from 20 to 40 cycles per second, but the efficiency drops rapidly above 40 cycles per second.

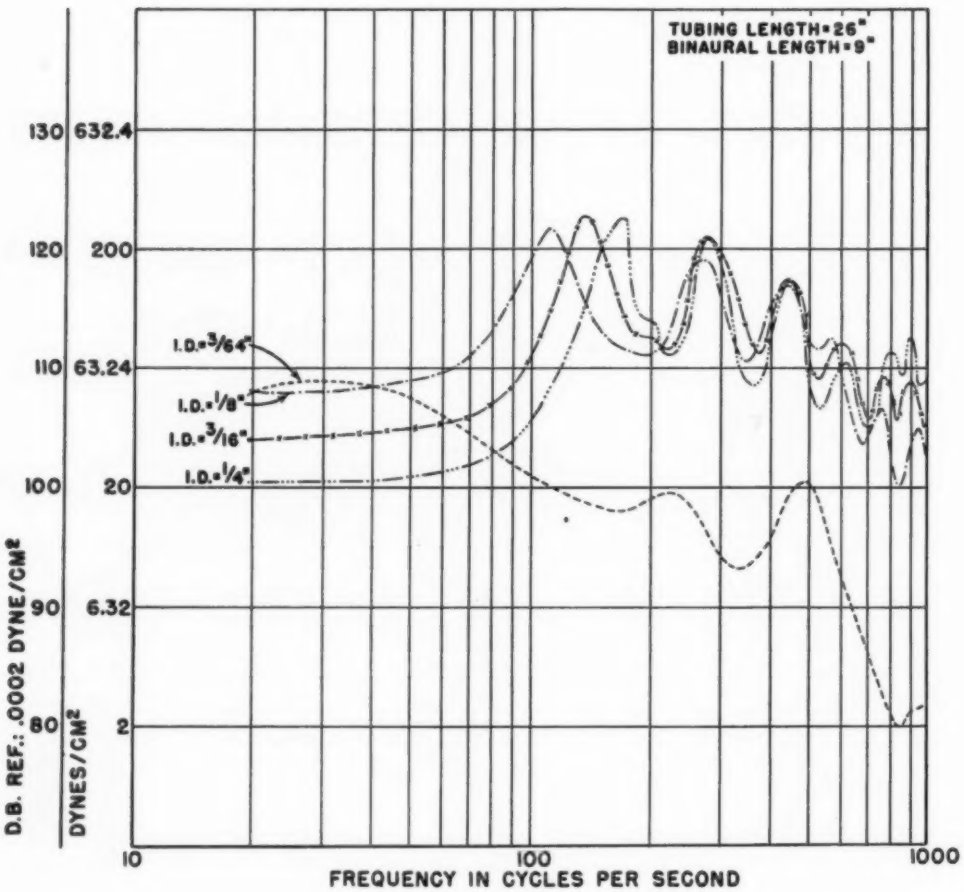

Fig. 3.—Response curves of an acoustic stethoscope in which the only variable is the bore or caliber of the tubing (I.D. =internal diameter).

3. In the low-frequency portion of the spectrum (20 to 115 cycles per second), the following auscultatory sounds generally fall: mitral diastolic murmurs, the low-pitched basal diastolic murmurs, the first, second, and third heart sounds, some systolic murmurs, and the auricular sound. The usual commercial stethoscope tubing, which has a 3/16 inch bore,

is less efficient between 20 and 115 cycles per second by a very appreciable number of dynes per square centimeter of sound pressure which is applied to the observer's ears.

4. Resonant peak displacement occurs for tubing of equal lengths but different caliber. The smaller the caliber, the lower is the frequency of the first resonant peak; the same pattern persists thereafter.
5. Between 200 and about 750 cycles per second, the difference in efficiency is not as large, although the 1/8 inch tubing seems to have a slight advantage. This portion of the auscultatory spectrum includes the high- and medium-pitched murmurs.
6. Above 750 cycles per second, the tubing with the ¼ inch bore becomes most efficient, and the 3/64 and 1/8 inch tubings are least efficient. This portion of the frequency spectrum has negligible utility in cardiac auscultation. Râles do have some frequency components in this portion of the spectrum.

CONCLUSIONS

1. It has been customary to use 3/16 inch caliber stethoscope tubing of varying lengths. Our data conclusively show that 1/8 inch caliber tubing produces a stethoscope of much higher efficiency except in a range that has practically no effect in cardiac auscultation.

2. The efficiency of a stethoscope increases as the tubing is decreased in length. If the tubing is made too short, the stethoscope becomes difficult to handle. Our experience has shown that a 10 inch length of rubber tubing is optimal for handling.

3. A 1/8 inch bore in the metal binaurals instead of the usual 3/16 inch will further increase stethoscope efficiency.

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Clinical Reports

CONGENITAL ANEURYSMAL DILATATION OF THE ASCENDING AORTA ASSOCIATED WITH ARACHNODACTYLY

An Angiocardiographic Study

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Jerusalem, Israel

ANEURYSMAL dilatation of the ascending portion of the aorta has recently been described as a congenital anomaly,[1] a diagnosis established by post-mortem examination. In the following paper, a case is reported in which this diagnosis was entertained during life with the aid of angiocardiographic and clinical observations. Furthermore, this patient presented a radiographic and clinical problem as to the nature of a filling defect in the lumen of the descending aorta during the angiocardiographic study.

CASE REPORT

J. R., a 27-year-old, unmarried woman, was admitted to the Department of Internal Medicine of the hospital on Nov. 30, 1949, because of intermittent bouts of fever accompanied by loss of strength and weight for the preceding four years. Family history was negative except for the death of two brothers at the age of 4 months and 3 years, respectively, of causes unknown to the patient.

Past History.—During childhood, the patient had scarlet fever. In 1937, at the age of 15 years, she had tonsillitis.

Present Illness.—In June, 1946, the patient began to complain of general malaise. A few weeks later fever appeared, and the patient was admitted to a hospital. During her hospitalization, her temperature ranged between 38° and 39° C. The patient complained from time to time of pains in the joints of the extremities, but there was no tenderness or swelling. She was treated with amidopyrine with no effect. Injections of penicillin were given, and her temperature gradually dropped to normal. According to the patient, an x-ray examination of the heart revealed a dilated aorta. The patient was discharged from the hospital but continued to suffer from general weakness.

About three months after her discharge, the fever reappeared. At this time, she complained of palpitation; there were no dyspnea or symptoms of heart failure. She was again admitted to a hospital. Wassermann tests in blood serum and in cerebrospinal liquor were negative. She was treated with penicillin with a beneficial effect and discharged from the hospital. From this time, there were three episodes of fever, each lasting for about three months and ranging from 37.5° to 39° C., accompanied by general malaise and diffuse pains in the extremities. During the entire course of the disease, blood cultures were repeatedly negative. An x-ray examination of the heart in February, 1948 (Fig. 1) revealed an enlarged mediastinum, most probably due to a distended aorta. The exact data are lacking because the patient was treated in various hospitals abroad.

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Physical examination on admission to the Rothschild-Hadassah University Hospital in Jerusalem revealed an asthenic, 27-year-old woman, weighing 39 kilograms. There was conspicuous pallor, and the face showed a typical "café au lait" color. No glands were palpable. The extremities were slender; the fingers were long and showed pronounced hyperextensibility.

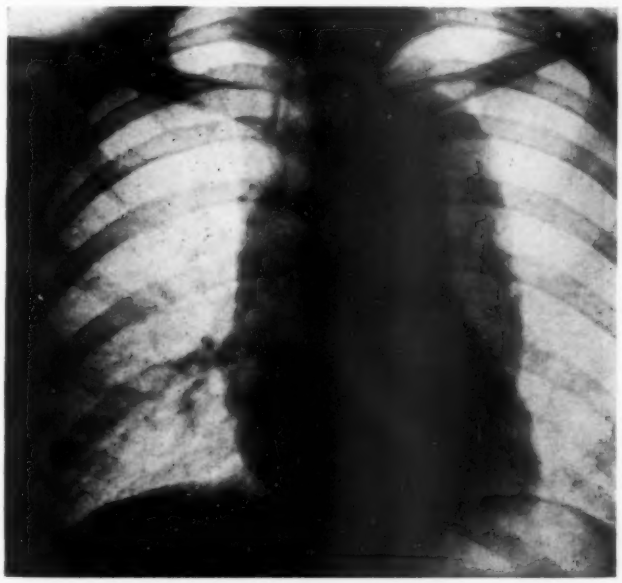


Fig. 1.—February, 1948. Conventional roentgenogram: The mediastinal shadow is markedly enlarged; the heart shadow is not enlarged.

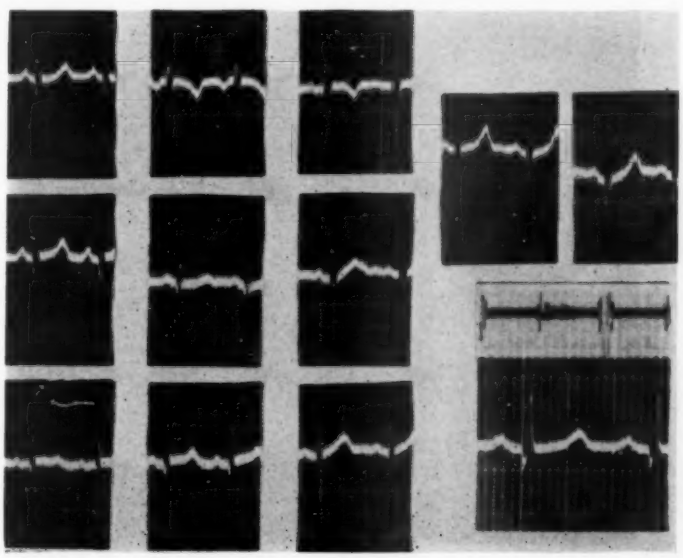


Fig. 2.—The electrocardiogram shows a normal pattern, the electrical position of the heart being intermediate. The phonocardiogram shows a systolic murmur. (For description see text.)

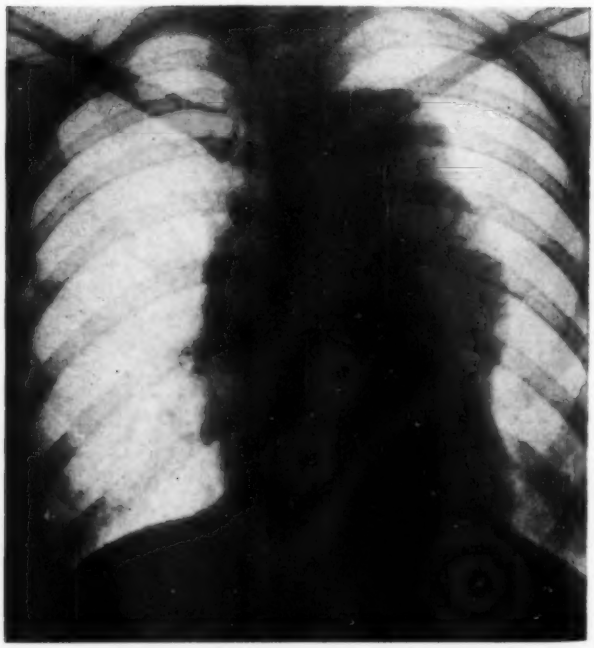
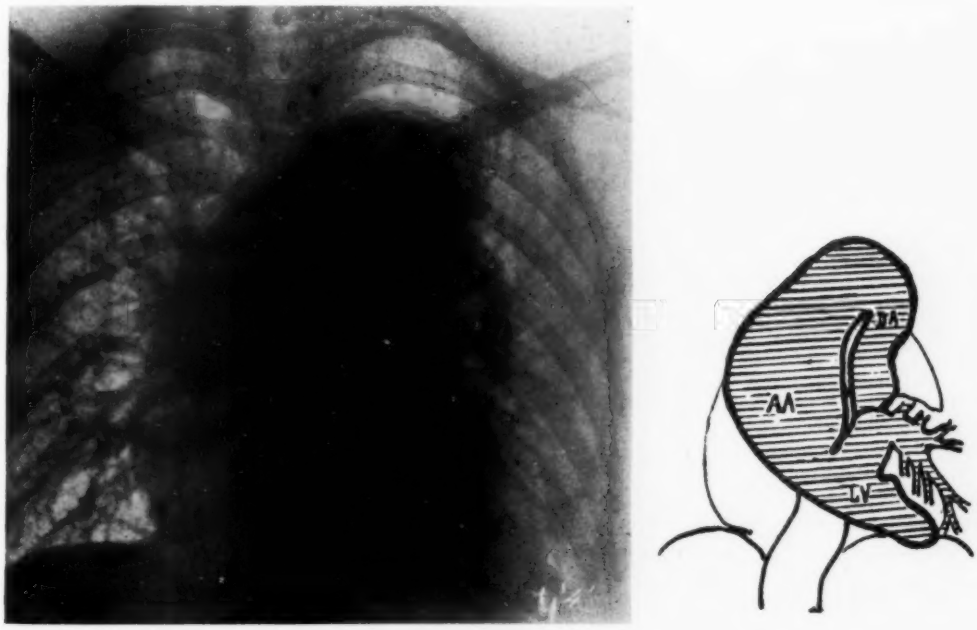


Fig. 3.—December, 1949. Conventional roentgenogram: The mediastinal and heart shadows are essentially of the same size and configuration as the previous roentgenogram in February, 1948. In addition, note a caplike prominence which is in continuity with the left mediastinal border.

Fig. 4.—Angiocardiogram (dextrogram made 2 seconds after beginning of the injection): The superior vena cava, the right atrium and ventricle, and the pulmonary artery and its branches are outlined.

The pupils were normal and reacted promptly to light and accommodation. The chest configuration was normal. The borders of the heart were normal; the apex beat was palpable just outside the mid-clavicular line at the fifth left intercostal space. The sounds were of normal quality; there was no thrill. A low-pitched systolic murmur of medium intensity was heard at the base of the heart with maximum intensity to the left of the sternum. The murmur was transmitted to the vessels of the neck and was well heard between both shoulders (see phonocardiogram, Fig. 2). The lungs were normal. The spleen was palpable below the costal margin. The patellar and Achilles reflexes were normal. The blood pressure in the left arm was 115/90 mm. Hg, in the right arm 125/90 mm. Hg, and in the legs 125/90 mm. Hg. An oscillometric examination of the arms and legs did not reveal any abnormal changes.



A. B.

Fig. 5.—Angiocardiogram (levogram made 4 to 5 seconds after injection): The pulmonary veins, the left atrium, the left ventricle, and the dilated ascending aorta are visualized.

The urine examination was negative. Serum albumin, globulin, urea nitrogen, and sugar were within normal range. Wassermann and Kahn tests of the blood serum and cerebrospinal liquor were negative. The sedimentation rate was 70/108 (Westergren); the blood count showed 3,800,000 erythrocytes, 7,000 leucocytes with 64 per cent segmented forms, 9 per cent stab forms, 22 per cent lymphocytes, and 5 per cent monocytes, and hemoglobin of 11.0 Gm. The circulation time (Decholin) was 12 seconds. Basal metabolism was −8 per cent.

The electrocardiogram (Fig. 2) showed a rate of about 100, a P-R interval of 0.16 second, and normal P waves. The ventricular complexes presented a small Q in the three limb leads, a slight elevation of the S-T interval in Leads II and III, and normal upright T waves. The unipolar leads were of normal configuration. The interpretation of this tracing was sinus rhythm and an intermediate position of the heart. It was thought to be within normal limits.

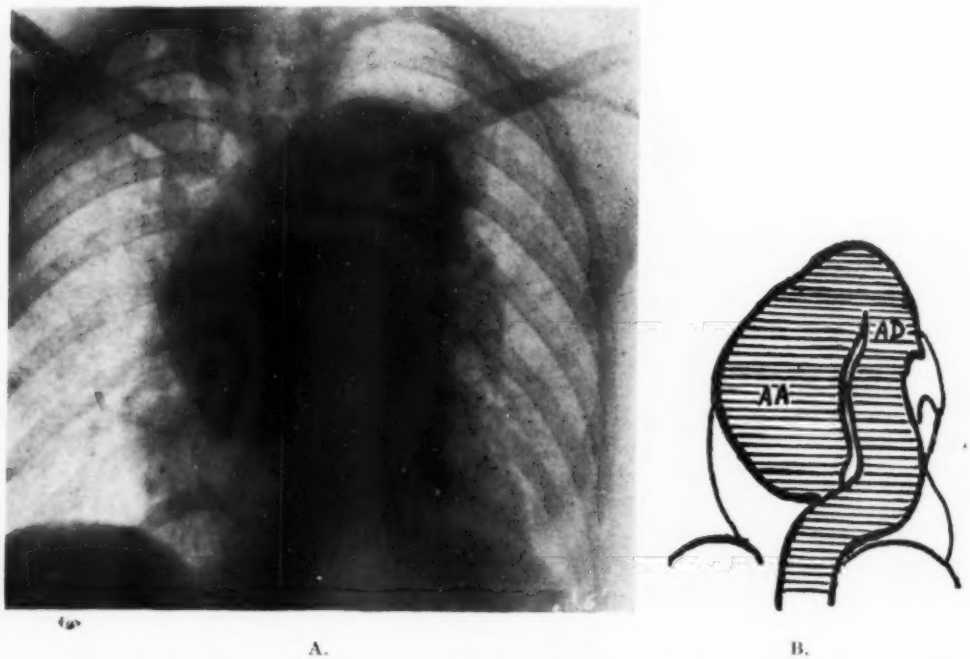
On fluoroscopy, the shadow of the mediastinum was markedly enlarged with a localized caplike prominence at its left border. The outlines of the bulge were in continuity with the left border of the mediastinal shadow. Only a slight pulsation was visible at the aortic arch segment. The left heart was not enlarged. The barium-filled esophagus was not deviated; the normal aortic indentation was seen. The roentgenogram (December, 1949, Fig. 3) confirmed the fluoroscopic impression. No notching of ribs was visible. The conventional x-ray examination to dif-

ferentiate a possible mediastinal process from an aneurysmic dilatation of a large vessel was not conclusive. An intravenous angiocardiographic examination (Diodrast 70 per cent) was therefore done. The following are the findings of the angiocardiogram:

A. Dextrogram (Fig. 4): The superior vena cava, the right atrium and ventricle, the pulmonary artery and its branches were outlined.

B. Levogram (Fig. 5): The pulmonary veins, the left atrium, the left ventricle, and the dilated ascending aorta were clearly visible.

C. Aortogram (Fig. 6): The contrast medium outlined the relatively narrow aortic conus. The aneurysmic ascending aorta, the aortic knob, and the descending aorta were visualized. Note the clear-cut filling defect at the lateral lumen of the descending aorta where the bulging was localized.



A. B.

Fig. 6.—Angiocardiogram (aortogram made 8 seconds after injection): The contrast medium outlines the relatively narrow aortic conus, the aneurysmic ascending aorta, the aortic knob, and the descending aorta. Note the clear-cut filling defect at the lateral aortic lumen of the descending portion, the site of the localized caplike prominence. The bulge continues smoothly into the aortic contour.

Course in the Hospital.—During the first week, the temperature ranged between 37° and 38° C. There were no embolic phenomena. After this period, although repeated blood cultures were negative, treatment with penicillin and streptomycin was instituted; 2,000,000 units of penicillin and 1.5 Gm. of streptomycin were given daily for a period of nineteen days. The temperature dropped to normal immediately after the beginning of the treatment. The general condition improved, the pallor disappeared, and the patient gained 2 kilograms in weight. The number of erythrocytes increased to 4,580,000, but the sedimentation rate remained rapid (76/100, Westergren). The patient was discharged from the hospital on Jan. 2, 1950. For three months following discharge, there was no recurrence of fever, but then low-grade temperature appeared. She was again treated with penicillin and streptomycin with beneficial effect.

DISCUSSION

The prominent features in this case were the recurrent attacks of fever during four years, which were apparently beneficially influenced by antibiotics, in a

patient having an enlarged mediastinal shadow. An additional localized bulging had developed in the period between February, 1948 (Fig. 1), and December, 1949 (Fig. 3), as seen in the radiographic examinations. These features suggested several possibilities: aneurysm of the aorta, adenopathy of the mediastinum, and tumor of the mediastinal organs. The fact that at fluoroscopy the shadow showed only a slight pulsation did not exclude the possibility of an aneurysm, since a thrombus formation may interfere with the pulsation.

Diffuse dilatation of the ascending aorta is sometimes seen in the adult type of coarctation. This diagnosis could be ruled out since there was no difference of blood pressure in the upper and lower extremities, and since there was no clinical or roentgenologic evidence of collateral circulation. Furthermore, graphic registration of the pressures from the carotid artery and the femoral artery simultaneous with the heart sounds revealed the normal delay at the femoral artery.

Other diagnostic possibilities were aortic and subaortic stenosis. The absence of left ventricular hypertrophy at the x-ray examination and in the electrocardiogram was evidence against this possibility. It seemed to us, also, that the dilatation of the aorta was more extensive than usually seen in these conditions.

Another condition to be considered was valvular heart disease, rheumatic or congenital, with mycotic embolism in the aorta causing an aneurysmal dilatation. It was difficult to accept this hypothesis since an affection of the valve could not be established on clinical grounds, and since the dilatation of the aorta was present at the start of the illness. Syphilitic aortitis was ruled out by negative clinical and laboratory findings.

Our case is fairly similar in its clinical features to those described by Baer, Taussig, and Oppenheimer.[1] In their patients the diffuse dilatation of the aorta affected especially the ascending part while the arch and the descending part were less dilated. This dilatation was due to a congenital abnormality of the media, which involved the muscular tissue and the elastic lamella. At histologic examination, these authors found rarefied and irregular muscle bundles and between these malformed muscle bundles large cystic spaces filled with a blue-staining coagulum. The media was further distorted by numerous irregular blood channels, which arose in the adventitia and invaded the media. There was no evidence of any inflammatory process or necrosis. The presence of arachnodactyly points, too, to the congenital origin of this condition, since it is frequently seen in congenital malformation of the heart.

In the case here presented, it had to be assumed that the aneurysmal dilatation of the ascending aorta was the primary site of the infection, the bacterial vegetation developing upon the intima of the aorta. The clinical course of this bacterial arteritis was essentially identical with that of a subacute bacterial endocarditis.

The clear-cut filling defect in the lumen of the descending aorta during the angiocardiographic study is most probably explained by a thrombus in the wall of the vessel which is the site of mycotic invasion. Another speculative thought was that of a localized dissecting aneurysm, but there was no history of a sudden excruciating pain.

SUMMARY

This is a report of the clinical, roentgenographic, and angiocardiographic observations on a patient who apparently had congenital aneurysmal dilatation of the ascending aorta.

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A CASE OF TRUNCUS ARTERIOSUS COMMUNIS COMPATIBLE WITH FULL-TERM PREGNANCY

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TRUNCUS arteriosus communis is a congenital malformation of the heart in which a single great vessel of abnormally large caliber combines the features of both great vessels; it receives all the blood from both ventricles and directs the blood both to the systemic circulation and to the lungs. The circulation to the lungs is established either by way of the pulmonary arteries which branch off directly from the base of the single great vessel or by pathways of the collateral circulation (to the lungs), usually by way of the bronchial arteries. The coronary arteries arise from the base of the common trunk which continues as the aorta and supplies the systemic circulation in the normal manner.[1] The condition is a rare type of congenital abnormality of the great vessels, and the prognosis is extremely poor, the vast majority of such patients dying in the first few weeks of life. When, as in this case, the pulmonary arteries are given off the descending aorta, individuals have been known to reach maturity.[1,2,3] Precise developmental, embryological, and pathological data were reported by Humphreys.[2]

The longest recorded survival was reported by Carr, Goodale, and Rockwell[4] whose patient, a man, lived to be 36 years and 2 months of age. A small number of cases have been reported of patients reaching maturity.[5-11] Many authors have reported survivals varying from minutes to weeks or months.[12-47] Causes of death in patients reaching maturity have included exertion,[4] subacute bacterial endocarditis,[6] and severe trauma following an automobile accident.[5]

To our knowledge no case of truncus arteriosus communis in association with a full-term pregnancy and delivery of a normal infant has been reported.

CASE REPORT

S. B., 19-year-old, white, para 0, gravida i, was admitted to the obstetrical service of the Jewish Hospital on Feb. 29, 1948. A diagnosis of congenital malformation of the heart was made during her infancy.[48] Cyanosis and dyspnea on exertion were present throughout life, but despite this she lived fairly normally. She was seen at frequent intervals from 1937 until 1945, during which time a systolic murmur was heard at the apex. No palpable thrills or irregularities of rhythm were ever noted. Chest x-ray, electrocardiographic, and fluoroscopic examinations during this period revealed right axis deviation, a heart in a transverse position, and dextroposition of the aorta (see Figs. 1 and 2). Nine months prior to admission, she became pregnant against the advice of her physician and refused therapeutic interruption of the pregnancy. The only complaint during pregnancy was shortness of breath. The blood pressure was 120/70 mm. Hg until the last two months of pregnancy when it rose to 160/90 mm. Hg. No other abnormal symptoms or signs were found.

From the Department of Clinical Laboratories, Jewish Hospital, Cincinnati.
Received for publication Sept. 8, 1950.

Physical examination on admission revealed a well-developed, well-nourished, 19-year-old woman in active labor. The only positive findings were slight cyanosis and minimal clubbing of the finger tips. She received 100 mg. of Demerol Hydrochloride approximately one and one-half hours before delivery and was delivered of a 4 pound male infant by low forceps and nitrous oxide and ether anesthesia. The placenta was delivered by manual Credé. There was excessive bleeding, and the patient received 1/160 gr. of Ergotrate and 10 units of Pituitrin in the delivery room. Eight hours post partum she continued to bleed. The uterus was packed, and a superficial laceration of the cervix was sutured. Bleeding stopped, and the pack was removed twenty-four hours later. She was given penicillin (50,000 units) at three-hour intervals following packing. During the morning of the third day post partum, the patient was feeling well except for a slight headache and a tachycardia of 110. Following a voluminous bowel movement, the patient suddenly collapsed and lost consciousness. She was given oxygen, artificial respirations, caffeine, and intracardiac Adrenalin to no avail and died within a few minutes.

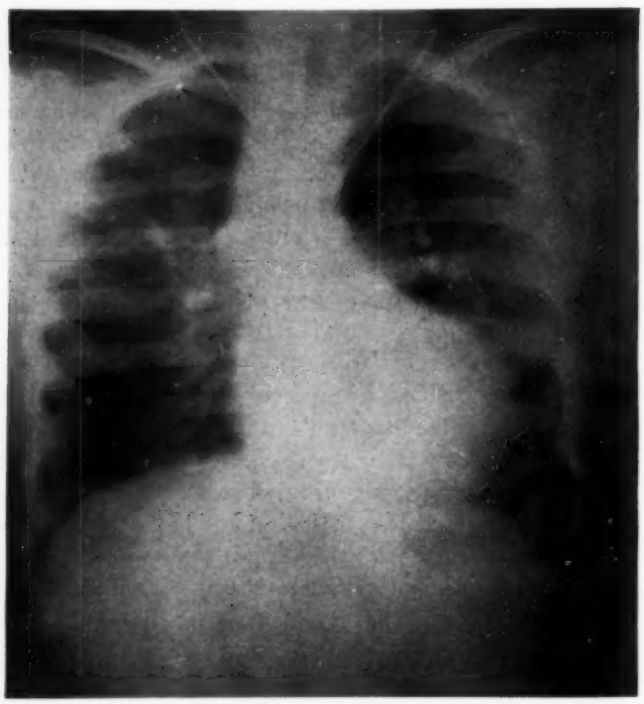

Fig. 1.—Chest teleroentgenogram revealing enlargement of left ventricle, trachea, and esophagus on left side of aortic arch and enlarged hilar shadows.

At post-mortem examination the primary pathologic diagnoses were truncus arteriosus, recent post-partum state with beginning involutional changes in the uterus and hyperplasia of the breasts, and areas of recent pulmonary infarction. The probable cause of death was recorded as a recent pulmonary infarct in a post-partum patient with congenital heart disease. The findings relative to the heart and great vessels were as follows: On opening the thoracic cavity the heart was seen to lie in a transverse position with a single large artery arising from its base. It weighed 390 grams. The following measurements were taken following Formalin fixation:

Circumference of tricuspid ring	8 cm.
Circumference of truncus arteriosus	6 cm.
Circumference of mitral ring	8.5 cm.
Size of interventricular defect	3 by 1 cm.

Length of right ventricle	5.5 cm.
Length of left ventricle	6 cm.
Thickness of right ventricular wall	12 to 14 mm.
Thickness of left ventricular wall	12 to 15 mm.
Circumference of pulmonary vessel arising from descending aorta	17 by 13 mm.
Circumference of secondary pulmonary vessel immediately below this	5 by 4 mm.

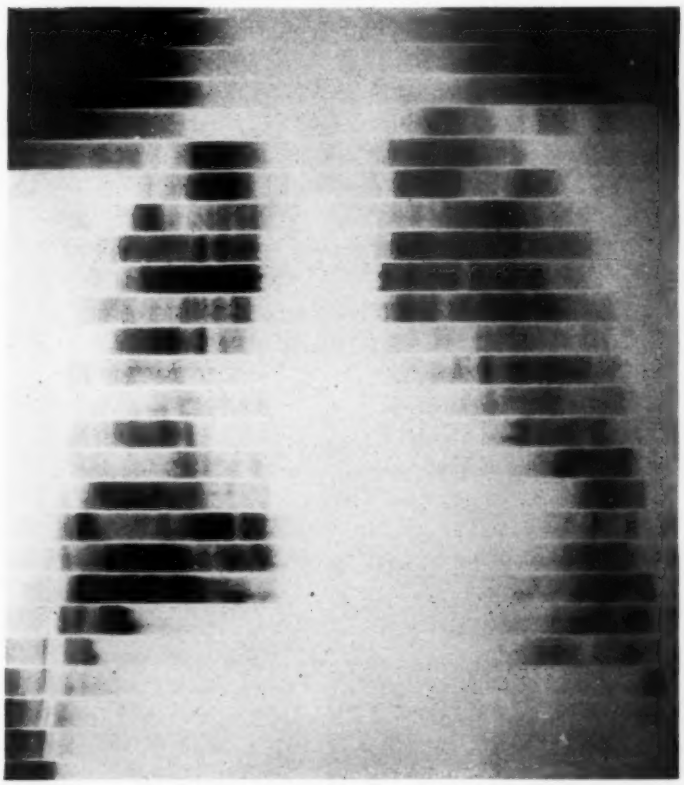

Fig. 2.—Roetgenkymogram reveals aortic arch on the right side of trachea as shown by pulsations.

The subepicardial fat was about average in amount. When the heart was opened, the right auricle was moderately dilated. The superior and inferior venae cavae were normal. The auricular wall was slightly thickened. The foramen ovale was anatomically patent but was apparently physiologically occluded. Tricuspid valve leaflets were thicker than average with chordae tendineae of one leaflet slightly thickened and fused. The mitral valve and its papillary muscles and chordae tendineae were normal. A large common truncus arteriosus arose almost completely from above the right ventricle. However, a small portion of the left side of this common arterial trunk originated over the interventricular defect and the left ventricle. The cusps guarding this artery were three in number. There was considerable widening of the commissures between the cusps, and a minimal amount of fibrosis and nodularity was noted. The three cusps were grouped as one anterior cusp and a right and a left posterolateral cusp.

One coronary artery was seen to arise behind the anterior cusp and another behind the left posterolateral cusp. The anterior coronary artery, after arising behind the anterior cusp, passed

to the right between the atrium and the right ventricle. It gave off a posterior descending branch which followed the interventricular septum to the apex along the posterior surface of the heart. The main branch continued along the left atrial ventricular sulcus apparently anastomosing with the terminal branches of the other coronary vessels. The left lateral coronary vessel was seen to extend between the right atrium and the common arterial trunk, giving off an anterior descending branch which traversed the anterior interventricular septum to the apex; this continued in a circumflex manner, coursing to the left between the left atrium and the left ventricle posteriorly to the base of the heart.

Fig. 3.—Anterior view of heart with hypertrophied right ventricular wall laid open revealing interventricular defect, truncus arteriosus communis guarded by three cusps. A probe projects into the right ventricle from the left ventricle.

The right ventricle was found to be markedly thickened and hypertrophied. The papillary muscles in this ventricle were thickened and prominent. The endocardium of the left auricle and left ventricle, although slightly thickened, was otherwise normal. The myocardium was of good consistency and color. The left ventricular wall was hypertrophied. The septum was thickened. The septal defect was prominent. Nothing suggestive of recent myomalacia or appreciable old scarring was seen.

Fig. 4.

Fig. 4.—Enlargement of descending aorta showing orifices of the two arteries leading to the lungs.

Fig. 5.—Enlargement of interventricular defect and valve leaflets guarding the single great vessel arising from the base of the heart.

The common arterial trunk formed its arch, giving off the right innominate, left common carotid, and left subclavian arteries in a normal manner. However, the arch remained on the right side, and the aorta was seen to lie to the right of the esophagus and trachea. The descending portion of the aorta passed behind the right main stem bronchus, and, arising from this descending portion of the aorta, the pulmonary artery came off at right angles and at the level of the bifurcation of the trachea. One and one-half centimeters beyond its origin and above the right main stem bronchus, this common pulmonary artery divided into the major right and left branches. The left branch passed to the left and in front of the bifurcation from its point of origin to the left hilum and measured 7 cm. in length and approximately 1.25 cm. in circumference. The pulmonary vein on the left showed no abnormalities. The left pulmonary artery remained dilated beyond its entrance into the lungs, and secondary and tertiary branches remained more prominent than average. The right lung was supplied by three arteries, that is, the main right stem branch of the common pulmonary artery, a smaller branch arising from the common pulmonary artery, and an independent branch coming off the descending aorta 1.5 cm. below the common pulmonary vessel. All of these arterial trunks were dilated more than normal following their entrance into the lungs. The secondary and tertiary branches were also dilated. A minimal amount of plaque formation was found in the intima of all the larger branches. The remaining gross findings and the microscopic examination revealed little additional information of importance.

SUMMARY

A case of truncus arteriosus communis is presented which was compatible with a full-term pregnancy and delivery of a normal infant. The infant showed signs of immaturity which were believed to be due to anoxia secondary to a congenital heart disease of the mother. The infant was a normal, healthy, growing child at the time of this writing, and examinations have revealed no evidence of disease.[48]

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MYOCARDIAL INFARCTION IN WOLFF-PARKINSON-WHITE SYNDROME

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THE electrocardiographic confirmation of myocardial infarction in the presence of the Wolff-Parkinson-White syndrome has been difficult to obtain.[5,6,10] The bundle branch block configuration, it is maintained, will obscure the pattern of myocardial necrosis. The purpose of this paper is to present a case where the electrocardiogram was diagnostic of infarction in the presence of anomalous atrioventricular conduction. This individual was known to have had the Wolff-Parkinson-White syndrome for at least five years before the onset of a classical clinical episode of acute myocardial infarction. Fortuitously, in one of the tracings a spontaneous change occurred from anomalous atrioventricular excitation to periods of normal conduction. It was during these latter phases that unequivocal electrocardiographic evidence of myocardial infarction was noted. No case with a similar electrocardiographic pattern has been found in a thorough search of the literature.

The syndrome of short P-R interval and prolonged QRS complex was first defined as a clinical entity by Wolff, Parkinson, and White[1] in 1930. Wolferth and Wood[2] and Holzmann and Scherf[3] independently postulated the existence of an accessory pathway between the atria and ventricles, similar to the so-called bundle of Kent, as explaining the electrocardiographic findings. Originally, Wolff, Parkinson, and White believed they were dealing with the effect of excessive vagal tone. There have been others[4] who offered evidence that the syndrome had a physiologic basis. This syndrome has been considered benign except for the attendant dangers of recurring attacks of paroxysmal tachycardia.

CASE REPORT

F. S., a 56-year-old white, married woman, was referred to the Coney Island Hospital on April 13, 1950 by her family physician. He had noted that the lips were cyanotic, the systolic blood pressure had dropped 60 mm. Hg, and pulmonary edema was present.

There were no previous episodes of chest pain but a history of hypertension for ten years.

The physical examination on admission to the hospital revealed the following: temperature 100.2° F., pulse 90 per minute, respiration 22 per minute, blood pressure 130/80 mm. Hg. She was well developed, moderately obese, and not in acute distress. The pupils were equal and reacted to light. The tongue was moist and the pharynx clear. There were a few medium râles at the right base. The heart was not enlarged. The rhythm was regular. No murmurs, fric-

From the Medical Service of Dr. Aaron Cohen, Coney Island Hospital (Dr. M. Mensch, Director), Brooklyn.

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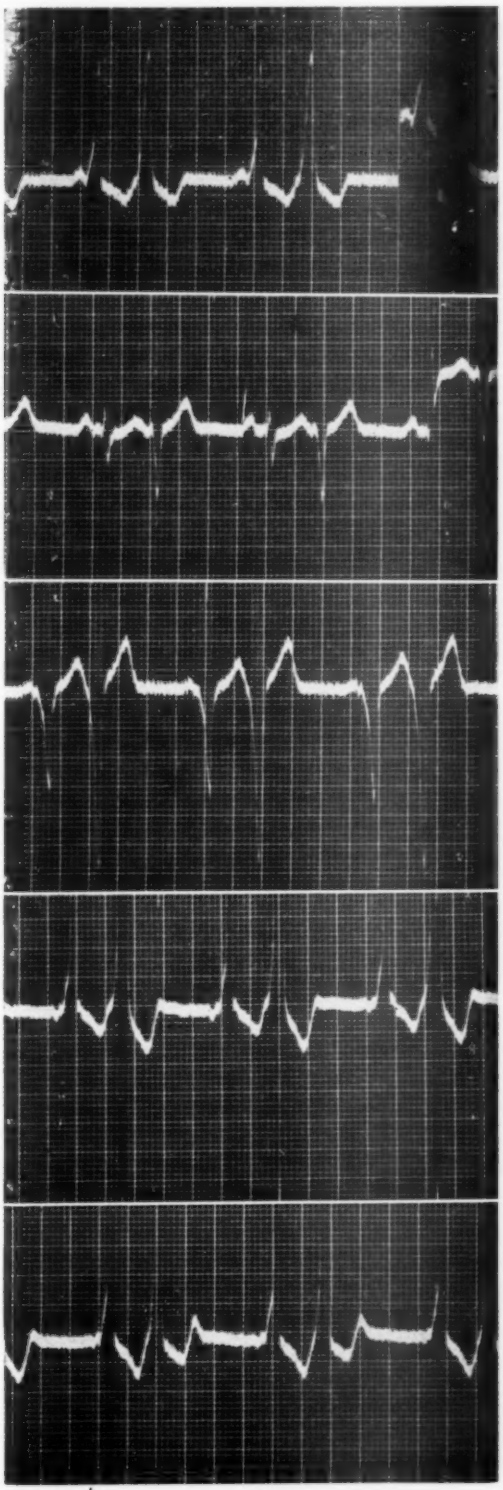

Fig. 1.

tion rub, nor gallop were audible. The abdomen was obese, but otherwise it was negative. There was no edema.

The laboratory studies were as follows: Urinalysis showed albumin and glucose negative, a specific gravity of 1.020, and a negative microscopic examination. Hemoglobin was 12.5 Gm. per cent, red blood cells 4,410,000, white blood cells 8,000, segmented polymorphonuclear leuco-

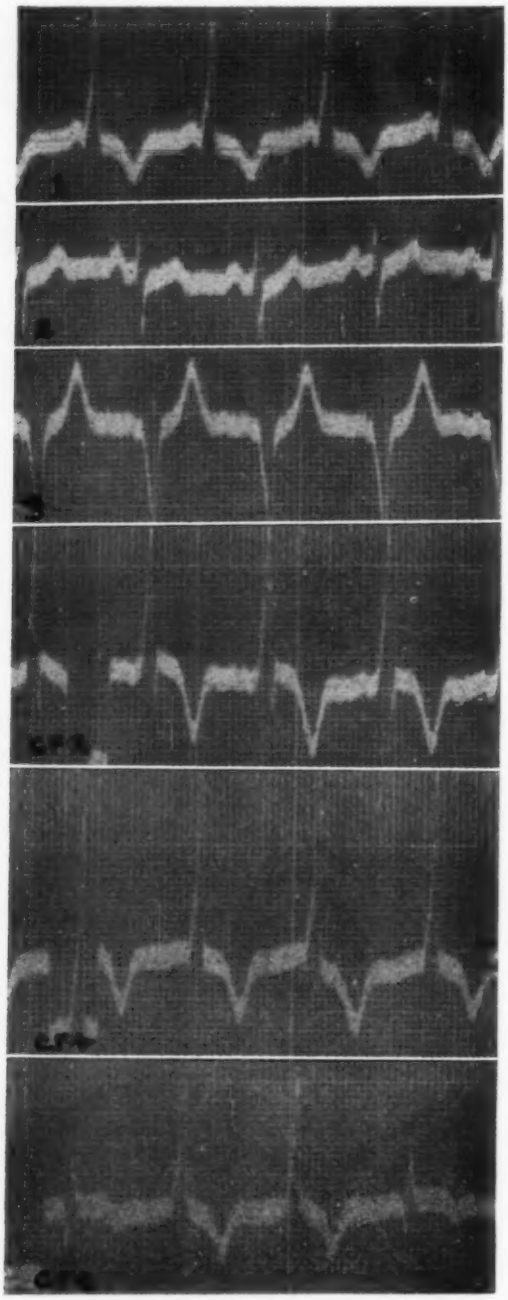

Fig. 2.

cytes 70, lymphocytes 28, eosinophils 2. The Mazzini serological test for syphilis was negative; fasting blood glucose was 153 mg. per cent; blood urea nitrogen was 12 mg. per cent. Erythrocyte sedimentation rate was 10 mm. per 1 hour, 2 mm., 17 mm., 8 mm., 3 mm. (normal 10 mm. per 1 hour).

Roentgenograms of the chest* revealed no cardiac enlargement. The aorta was elongated. The mediastinum was clear. The lung fields showed slight generalized congestion. No parenchymal pathology nor any fluid was noted.

A diagnosis of myocardial infarction was made, and the patient was placed on papaverine, Demerol Hydrochloride, and anticoagulants (heparin and Dicumarol).

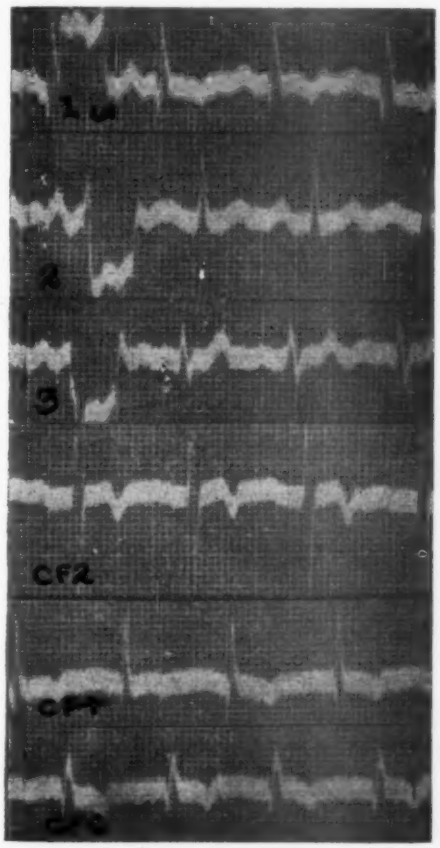

Fig. 3.

The temperature became normal thereafter, except for May 4, 1950, when it rose to 101° F. The blood pressure on admission was 130/80 mm. Hg; April 25, 160/90 mm. Hg; May 3, 160/100 mm. Hg; May 12, 195/100 mm. Hg.

The patient's course was marked by persistent substernal pressure which radiated to the back despite complete bed rest and sedation. On May 3, 1950, she complained of chest pain and palpitation. On auscultation a rapid and irregular rhythm was heard. However, an electrocardiogram was not obtained at the time. She was discharged improved on May 20, 1950.

Electrocardiographic Studies.—The first electrocardiogram (Fig. 1) was taken on Oct. 15, 1945, at which time the patient had no symptoms referable to the cardiovascular system.

*Interpretation by Dr. E. Mendelson.

The picture was that of a Wolff-Parkinson-White syndrome with a bigeminal rhythm. The P-R interval was 0.08 second and the QRS 0.12 second. The T wave was inverted in Leads I and $CF_{2,4}$. Left axis deviation and a deep QS_3 were present.

On April 13, 1950, while the patient was in the hospital regular sinus rhythm was noted. There were left axis deviation, a P-R interval of 0.08 second, and a QRS complex of 0.14 second; ST was depressed and the T wave inverted in Leads I and $CF_{2,4,6}$. There was a deep QS_3. The tracing of April 14 (Fig. 2) was essentially the same except that the T wave in $CF_{2,4,6}$ was deeper and more sharply inverted. In addition, there were noted, in CF_6, only several complexes where normal conduction prevailed. The QRS complex was 0.08 second; a deep Q wave and RT elevation and rounding with T-wave inversion were present. These findings were considered indicative of myocardial infarction.

Whereas the above two electrocardiograms were typical of the Wolff-Parkinson-White syndrome, on May 1 (Fig. 3) there was normal conduction. The auricular and ventricular rates were 88 per minute; rhythm was regular; the P-R interval was 0.18 second and the QRS complex 0.08 second. There were a Q wave and an inverted T wave in Leads I and $CF_{4,6}$. These clearly demonstrated the pattern of myocardial infarction involving the anterolateral wall. On May 9, normal conduction pathways were still present, and the only difference noted from May 1 was that T in Lead II was of lower voltage.

On June 12, 1950, about three weeks following the patient's discharge from the hospital, an electrocardiogram failed to show any evidence of infarction but was typical of the Wolff-Parkinson-White syndrome. The P-R interval was 0.09 second, the QRS was 0.12 second, and T-wave inversion was seen in Leads I, aV_L, and V_1 through V_6. A deep QS wave was found in Leads III and aV_F.

COMMENT

The diagnosis of the Wolff-Parkinson-White syndrome seems quite clear in this case. The episode of pain and palpitation on May 3, 1950 was probably due to a paroxysmal tachycardia, to which patients with the Wolff-Parkinson-White syndrome are so prone. The clinical picture of prolonged and severe anterior chest pain, collapse, marked drop in blood pressure, and low-grade fever in itself warrants a diagnosis of myocardial infarction. The initial electrocardiogram following the acute cardiac episode, demonstrating a shortened P-R interval and prolonged QRS complex, showed no evidence of myocardial infarction. The tracing of April 14, 1950, only in Lead CF_6 (Fig. 2), however, revealed the underlying disease of myocardial necrosis, so that the diagnosis of coronary thrombosis with myocardial infarction was now established from the electrocardiographic viewpoint. The tracings of May 1 (Fig. 3) and 9 where normal conduction occurred (the aberrant pathway between atrium and ventricle was apparently nonfunctioning) clearly showed in all leads the presence of an anterolateral myocardial infarction.

Previous reports of myocardial infarction superimposed on the Wolff-Parkinson-White syndrome have in the main been predicated on a more or less typical clinical story in an individual whose electrocardiogram showed a short P-R interval and a prolonged QRS complex. Rinzler and Travell[6] reviewed the literature and reported several cases of their own. They concluded that the diagnosis can be established only on the basis of criteria other than the electrocardiographic changes. Zoll and Sacks[7] reported a case of posterior wall

myocardial infarction in a patient with a short P-R interval and prolonged QRS complex in whom the T waves were inverted in Leads II and III. These later reverted to normal.

Eichert[8] reported a case of a 40-year-old man with a history of severe and protracted subpectoral pain and an electrocardiogram with a short P-R interval and a prolonged QRS complex. The diagnosis made at the time was myocardial infarction. An evaluation of all the factors over an eight-year period led the author to conclude, however, that the case was one of Wolff-Parkinson-White syndrome in a patient with neurocirculatory asthenia. He placed little significance on one tracing taken during a period of normal conduction where a Q wave and inverted T waves were noted in Leads II and III, findings suggestive of a posterior wall infarction.

Fischer[9] presented a similar case in which the diagnosis of myocardial infarction in a patient with Wolff-Parkinson-White syndrome was manifest by ST-T wave changes in Leads II and III. He insisted, however, that the clinical picture must confirm the diagnosis.

Dressler and Roesler[12] illustrated a case where beats of the Wolff-Parkinson-White type and normally conducted beats were both present, but only in the latter was there evidence suggestive of myocardial infarction (deep QS in $CF_{3,4}$). This case is similar to the one herein reported except that the electrocardiographic pattern was more that of an old infarction although the history was of recent origin, whereas in our patient the findings in the electrocardiogram indicated an acute lesion.

In an experimental study[10] Tamagna and co-workers artificially produced an auriculoventricular shunt with the resulting electrocardiogram showing a shortened P-R interval and a lengthened QRS complex. A coronary vessel was then ligated and the electrocardiographic response noted. The conclusion arrived at was that in small infarcts producing only T-wave changes, the electrocardiographic findings are insufficient to establish a definite diagnosis of myocardial infarction. They suggested that an attempt be made to convert the Wolff-Parkinson-White pattern to a normal conduction mechanism when myocardial infarction is suspected. This has been done by the administration of quinidine previously.[11] In the case we are reporting this is exactly what occurred spontaneously, and, as Tamagna and co-workers predicted, the true picture of myocardial infarction made itself quite evident. Our observation may be duplicated by others should sufficient serial tracings be taken.

CONCLUSIONS

A review of the literature pertaining to the presence of myocardial infarction in individuals with the Wolff-Parkinson-White syndrome is undertaken to which a case of our own is added. It has been generally held that bundle branch block obscures the electrocardiographic pattern of myocardial infarction and that therefore the diagnosis must depend in a large measure on the clinical picture. Our case is unique in that the spontaneous appearance of normal conduction

revealed the true electrocardiographic picture of myocardial infarction. It is recommended that frequent serial tracings be obtained in the hope that spontaneous appearance of normal conduction may be manifest.

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PAROXYSMAL VENTRICULAR TACHYCARDIA: EXPERIENCE WITH QUINIDINE HYDROCHLORIDE*

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JOSEPH REISS, M.D., NEW YORK, N. Y.

VENTRICULAR tachycardia occurs infrequently. Its appearance in patients with structural heart disease demands prompt and energetic treatment. Unless this abnormal rhythm is stopped, congestive failure eventually supervenes and leads to a fatal outcome.

There is a growing literature indicating the value of quinidine in the treatment of this abnormal rhythm. Yet there are few reports recording electrocardiographically the change-over from the abnormal rhythm to a sinus rhythm following the intravenous use of quinidine. In view of the paucity of such case reports, it was considered important to record a gratifying experience with quinidine hydrochloride in the treatment of ventricular tachycardia in a patient in whom the change-over from ventricular tachycardia to a sinus rhythm was recorded on the electrocardiogram.

CASE REPORT

A 55-year-old man with hypertension was treated successfully for approximately thirty months on a low-sodium regime.[1] Fig. 1,*A*, records the control electrocardiogram indicating a strain pattern. On May 22, 1950, the patient was seized with severe, crunching substernal pain. He became pale with profuse perspiration. The clinical diagnosis of coronary artery thrombosis with myocardial infarction was fortified by a drop in blood pressure, fever, leucocytosis, and an increase in the sedimentation rate. The electrocardiogram (Fig. 1,*B*), taken after a lapse of ten hours, demonstrated that a change in pattern had occurred. On the morning of the sixth day his condition was satisfactory. He awakened from his midmorning sleep and was fed his noonday meal. He took two mouthfuls of food and suddenly complained that everything seemed blurred. He blanched and broke out into a profuse and drenching sweat. His radial pulse was not perceptible. The nail beds were cyanotic. The heart tones were distant. The apical rate was too fast to be counted. An electrocardiogram was taken. Ventricular tachycardia with a ventricular rate of 214 was demonstrated (Fig. 2). One and one-half hours later, the clinical picture changed. He complained of squeezing substernal pressure. His pulse and blood pressure were unobtainable. The respirations were shallow. Râles were audible at the bases of both lungs posteriorly. He was in profound collapse. Coramine, Pantopon, and caffeine sodium benzoate were given subcutaneously. Quinidine (3 gr. capsule) was given orally. Three hours later the condition was unchanged. The radial pulse and the blood pressure remained unobtainable. He had not urinated since the onset of the tachycardia. The heart tones at the apex were extremely faint and were audible with difficulty; the rate was too rapid to count. The pupils were contracted (narcotic effect). Another electrocardiogram was taken. It was identical with that recorded in Fig. 2.

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Vagal stimulation in the form of carotid sinus and ocular pressure failed to influence the cardiac rate. The electrodes of the electrocardiograph were strapped into position and the dial set at Lead II. Quinidine hydrochloride, 0.6 Gm., and 15 per cent antipyrine in a sterile solution of urea was given slowly into the antecubital vein of the left arm. A stethoscope was held in place over the apex so that the heart tones could be heard during the administration of the quinidine. A continuous electrocardiogram was taken during the procedure. Within 53 seconds of the start of the injection the patient had a wave of nausea. A brief period of asystole was heard and was

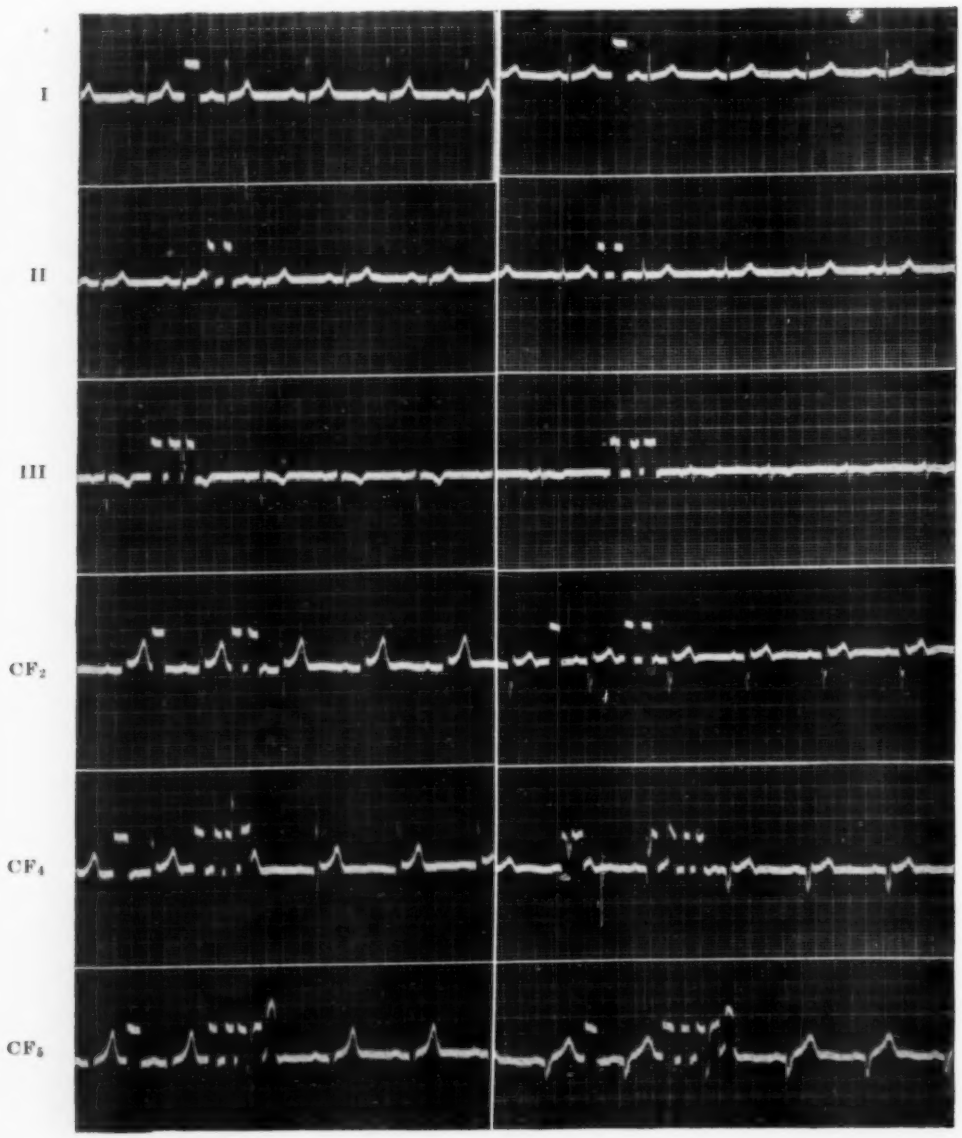

Fig. 1.—*A*, Control electrocardiogram taken May 13, 1950. *B*, Taken ten hours after the onset of the acute coronary episode, May 22, 1950. Note changes in Leads I and III, as well as in the precordial leads.

recorded on the electrocardiogram (Fig. 3). It was followed by a normal sinus rhythm. Almost immediately the radial pulse was palpable. The apical rate was 100, and the heart tones were clearly audible. The systolic blood pressure was 80 mm. Hg, and the diastolic pressure was 50. The cadaveric pallor was replaced by a slight pinkish blush. The perspiration ceased. Within

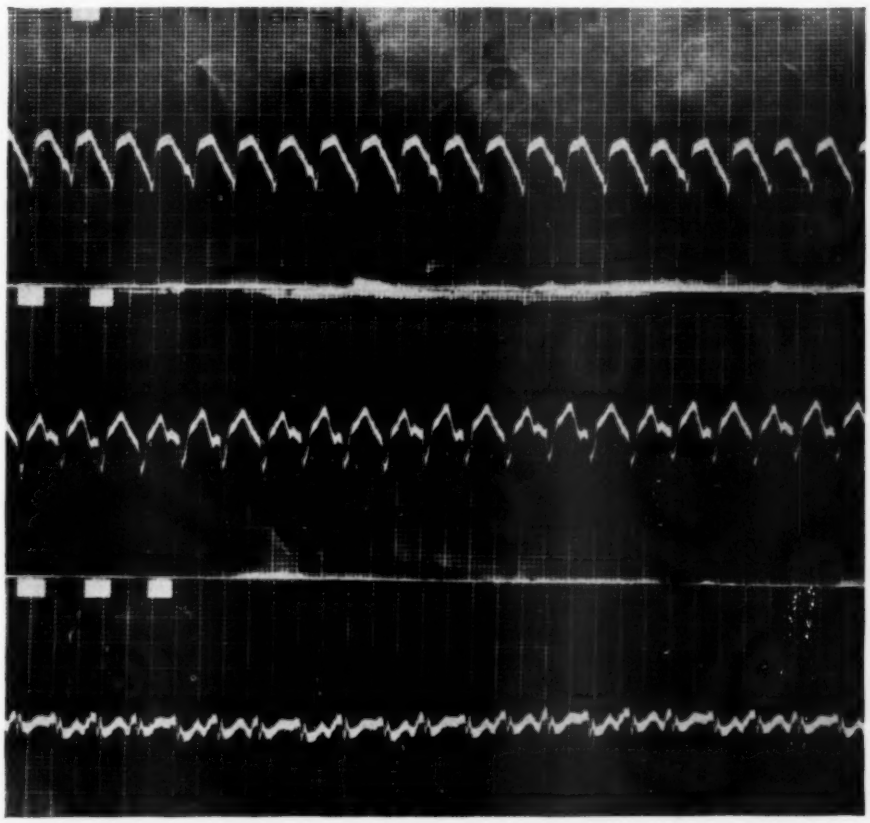

Fig. 2.—Electrocardiogram taken on May 28, 1950, demonstrating ventricular tachycardia with a ventricular rate of 214.

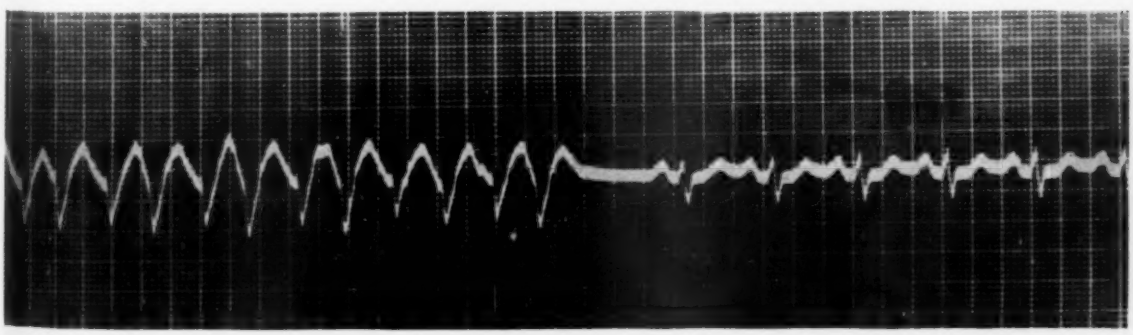

Fig. 3.—Electrocardiogram taken in Lead II, demonstrating the ventricular tachycardia, the period of asystole, and the resumption of sinus rhythm.

one hour the skin was dry, and the patient was sleeping quietly. The radial pulse was 102; the systolic blood pressure was 90 mm. Hg, and the diastolic was 65. The electrocardiogram (Fig. 4) revealed regular sinus rhythm. Convalescence was uneventful and recovery was complete.

Comment.—There are several points of interest in this case which are provocative of brief comment. Occasionally, ventricular tachycardia develops when there is no other detectable abnormality. More often, however, it is a manifestation

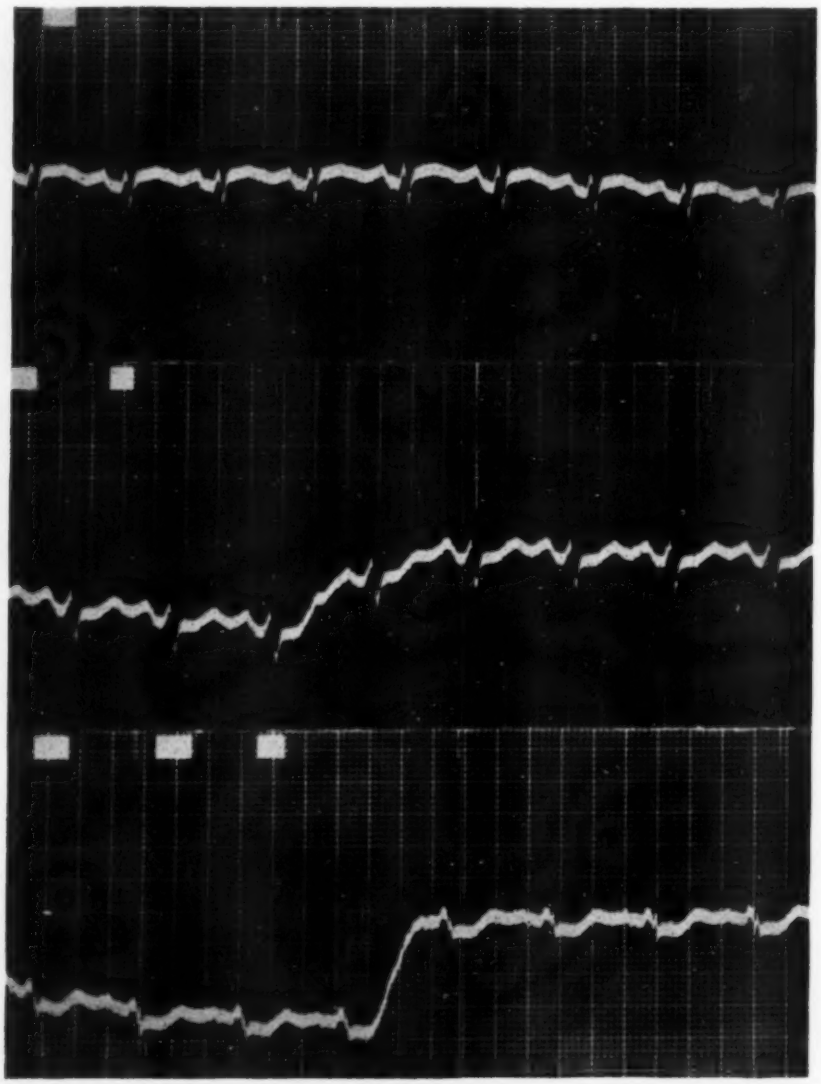

Fig. 4.—Tracing taken one hour after the injection of quinidine, demonstrating a normal sinus rhythm.

of organic heart disease in muscle previously damaged by myccardial infarction. diffuse myofibrosis, hypertension, rheumatic fever, or digitalis intoxication, Herrmann and Hejtmancik[2] have observed that heart muscle which is damaged may fail as a result of the sudden onset of an abnormally rapid rate. In the case

under consideration organic heart disease was present. The progressive downhill course which this patient followed and the severity of the peripheral collapse indicated that the ventricular tachycardia was a true medical emergency. Heroic measures were required to terminate the tachycardia and so prevent a lethal result. With full knowledge of the possible untoward effects, the intravenous route of administration of quinidine was decided upon. The result was dramatic. Since the change-over from ventricular tachycardia occurred 53 seconds after the start of the intravenous quinidine hydrochloride injection, it was concluded that the regular sinus rhythm was the result of this therapeutic procedure. One must be mindful of the fact that, on occasion, ventricular tachycardia will revert spontaneously to a sinus rhythm. Such a conversion can also follow the oral administration of quinidine. In this instance, however, we did not attribute the dramatic result recorded to either a spontaneous remission or to the effects of the single dose of quinidine administered orally.

Since it is important to interrupt an abnormally rapid heart action promptly if one is to avoid a lethal result, it is equally important that an accurate diagnosis be made promptly. The diagnosis of ventricular tachycardia is really made on the electrocardiogram. Robinson and Herrmann[5] have described the requisite diagnostic features. The presence of P waves may be difficult to detect in the standard limb leads. Their presence occurring independently and at a slower rate than the ventricular complexes is significant. The occurrence of ventricular complexes abnormal in form from those observed in the same patient when the paroxysm is not present is another significant feature. In addition, one occasionally notes the presence of isolated ectopic complexes during the paroxysm. The electrocardiogram in the case herein presented (Fig. 2) fulfills two of the above criteria. One notes the presence of the P waves occurring independently and at a slower rate than the ventricular complexes. In addition, the ventricular complexes were abnormal in form by comparison with those noted in the control as well as in the postparoxysm tracing.

SUMMARY

1. Ventricular tachycardia complicating a recent episode of myocardial infarction is reported.

2. The change-over from the ventricular tachycardia to the sinus rhythm was recorded electrocardiographically.

3. The beneficial effects of the intravenous administration of quinidine hydrochloride are reaffirmed.

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ADDENDUM TO "HODGKIN'S GRANULOMA WITH PERICARDIAL EFFUSION"

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THERE appeared in this JOURNAL (**40**:624-629, 1950) a case report under the above title. The patient died in January, 1951, and there is herewith recorded a report of the autopsy.

REPORT OF THE AUTOPSY

A. Gross Description.—The body was that of a young white man who was moderately well developed but poorly nourished. Examination of the axillae and inguinal regions revealed several discrete, palpable, "rubbery" nodes. One node in the left axilla measured 3.0 cm. in diameter. There was a large right cervical lymph node, just superior to the clavicle and in the posterior triangle, which measured 3.0 by 4.0 cm.

When the peritoneal cavity was opened, the liver was found to lie 8.0 cm. below the xiphoid process and below the right costal border. There was a small amount of clear peritoneal fluid present (75.0 c.c.). When the chest plate was removed, 500 c.c. of clear intrapleural fluid were found on the right side and 350 c.c. on the left side. The right diaphragm was at the level of the fifth interspace and the left diaphragm at the level of the sixth interspace. There were enlarged, "rubbery" lymph nodes spread diffusely throughout the anterior mediastinum and measuring 0.5 to 3.0 cm. in diameter. Similar nodes were also palpable on the inferior surface of the right diaphragm. Both right and left lungs were small, and on removal there was an additional pocket of 750 c.c. of clear fluid in the left chest. Medially, in the posterior mediastinum and the anterior mediastinum, involving the region anterior and posterior to the heart and both diaphragmatic pleural surfaces below, were large numbers of similarly enlarged lymph nodes. Attempts to remove the parietal pericardium were fruitless, for it was firmly adherent to the visceral pericardium. The pericardium was intimately involved by the large granulomatous mass which appeared as a fungating tumor, and which encroached on and involved the myocardium, but not the endocardium. The tumor nodules and mass had so distorted the heart that it was difficult to determine its anatomic landmarks. The majority of the right ventricle had been invaded and replaced by the new growth; the myocardium of the left ventricle was moderately well preserved. There was a generalized thickening of the epicardium and pericardium, which were completely involved by the granulomatous tumor. Both the right and left ventricles were dilated and moderately hypertrophied. The weight of the entire specimen, involving the heart and the surrounding mediastinal mass, was 1,300 grams. The myocardium of the left ventricle measured 1.5 cm. in thickness; the entire thickness including the epicardium and pericardial surfaces was 2.5 cm. The myocardium of the right ventricle measured 0.5 cm. in thickness, and the entire thickness including epicardium and pericardium was 2.0 cm. The granulomatous mass of tumor not only extended to involve the heart and pericardium, but also extended along the great vessels as they passed from the heart and entirely surrounded them. The mass itself was yellow-gray in color and consisted of numerous nodules closely matted together.

B. Microscopic Description.—

Heart: Several sections showed scattered nodules as well as diffuse sheaths of infiltrating tumor in the myocardium and pericardium of the auricles and ventricles. There was no evidence

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of involvement of the endocardium or the valves. This tumor was a sclerosing type of Hodgkin's disease, characterized by a mixture of reticulum cells, lymphocytes, plasmocytes, neutrophils, and eosinophils, with an abundant distribution of multinucleated giant cells of the Dorothy Reed type. There were occasional areas of necrosis, and there was an abundant fibrous stroma throughout, with some areas replaced by broad bands of fibrous tissue. One section showed involvement of the aorta near the heart.

Lungs: Hodgkin's disease in various stages replaced large portions of the lung parenchyma. This was diffuse, alveolar, bronchial, and peribronchial in distribution. Some areas showed marked fibrosis, calcific deposition, and hyalinization. There were also areas of necrosis. The architecture varied from the acute stage with diffuse reticulum-cell proliferation and numerous typical giant cells to the sclerosing phase with diffuse fibrosis and a network of collagenous stroma; some areas suggested the appearance of reticulum-cell sarcoma.

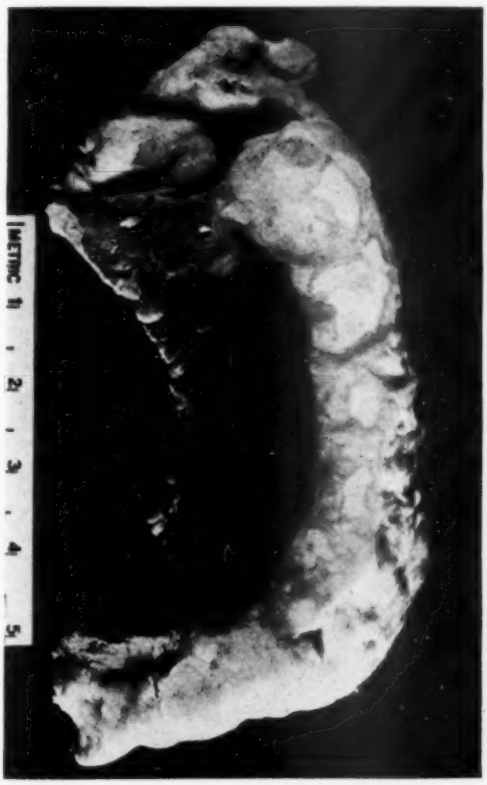

Fig. 1.—Photograph of a gross section through the heart showing infiltration of the pericardium by Hodgkin's granuloma.

Lymph nodes: There was partial to complete replacement of the normal lymph node architecture by the tumor of Hodgin's disease.

Mediastinal tumor: The appearance and invasion of the tumor was similar to the lung, infiltrating and surrounding blood vessels, nerves, and lymph nodes.

Bone marrow: There were focal areas of reticulum-cell proliferation and occasional plasma cells. There was no other evidence of Hodgkin's disease.

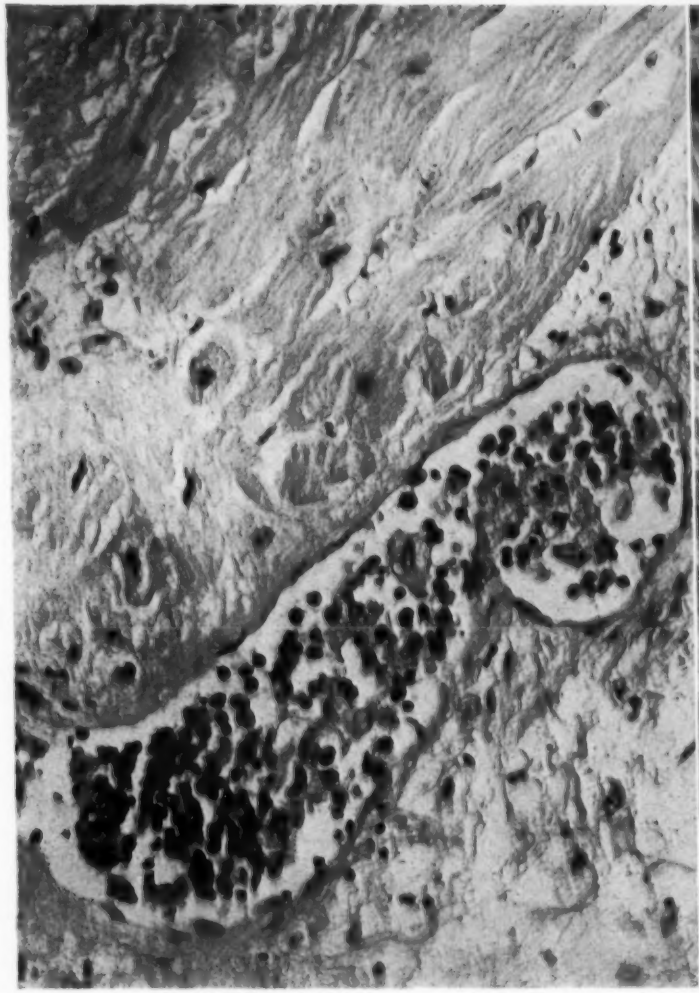

Fig. 2.

Fig. 3.

Fig. 2.—Photomicrograph of heart muscle showing Hodgkin's granuloma in the coronary sinus. (Hematoxylin and eosin stain, × 280.)

Fig. 3.—Photomicrograph of heart muscle showing Hodgkin's granuloma infiltrating the myocardium of the left ventricle. (Hematoxylin and eosin stain, × 220.)

Fig. 3.—Photomicrograph of heart muscle showing Hodgkin's granuloma infiltrating the myocardium of the left ventricle. (Hematoxylin and eosin stain, × 220.)

CLINICAL DIAGNOSES

The clinical diagnoses were:

1. Hodgkin's granuloma with involvement of lymph nodes, pericardium, lungs, and pleura
2. History of pericardial effusion

PATHOLOGICAL DIAGNOSES

The pathological diagnoses were as follows:

1. *Cardiovascular System*
   a. Hodgkin's disease of the pericardium, epicardium, and myocardium (auricles and ventricles)
   b. Ventricular hypertrophy and dilatation
   c. Adhesive pericarditis
2. *Respiratory System*
   a. Hodgkin's disease of the lungs, the pleurae, the diaphragm, and the mediastinum
   b. Bilateral hydrothorax
   c. Adhesive pleuritis
3. *Spleen and Hematopoietic System*
   a. Generalized Hodgkin's disease

The author's thanks and appreciation are due to Dr. Clara Raven and Dr. Paul Klingenberg, Department of Pathology, Veterans Hospital, Dayton, Ohio, for the report of the gross and microscopic findings of the autopsy, and to Dr. Emmerich von Haam, Department of Pathology, Ohio State University, Columbus, Ohio, for the photographs and photomicrographs and their descriptions.

Book Reviews

HEART: A PHYSIOLOGIC AND CLINICAL STUDY OF CARDIOVASCULAR DISEASE. By Aldo A. Luisada, M.D. Baltimore, 1948, The Williams and Wilkins Company.

In this monograph, the author has presented with clarity and brevity a broad review of cardiology. The work is well organized and illustrated. Emphasis is placed on physiology of the cardiovascular system and upon the pathologic physiology of cardiovascular diseases.

Much of the material presented is derived from the author's own experimental and clinical experience. Implications and conclusions from this source are at times emphasized at some variance with classical concepts.

The author's interest in phonocardiography and mechanism recording of cardiovascular phenomena is evidenced by the unusual amount of space devoted to these subjects. The summary of electrocardiography presents a review of basic principles and standard techniques, but it does not include unipolar methods.

R. P.

THE LOW FAT, LOW CHOLESTEROL DIET. By E. V. Dobbin, H. F. Gofman, H. C. Jones, L. Lyon, and C. Young. Garden City, N. Y., 1951, Doubleday & Co., Inc., 371 pages.

To prescribe a special diet is relatively simple. To ensure that the patient can obtain and eat that diet is more difficult. This book provides the information needed to ensure that patients can obtain and eat a low fat, low cholesterol diet. It is not primarily concerned with possible indications for the prescription of that diet.

The text is based on experiences with the low fat, low cholesterol diet at the University of California; its authors comprise two dietitians, a home economist, a housewife, and a physician. Material presented includes selection and methods of preparation of foods, recipes, menus, and sources from which less familiar foods can be purchased. Details, such as choosing lunch in restaurants, box lunches, sandwiches, appetizers, and snacks, are not overlooked. The nutritional basis of the advice offered is explained in appropriate places throughout the text. The appendix contains an additional discussion of nutritional aspects and relevant tables of food values. General and recipe indexes are provided.

If the low fat, low cholesterol diet comes into common use, the authors will have rendered a notable service by setting forth so clearly and in such useful detail the results of their experience. Dietitians will find the book invaluable, and it will be helpful to physicians who prescribe this diet. Wide use by patients seems unlikely. Many have not the interest, intelligence, mental discipline, or educational background required to study and learn from a book. For those who can use it with profit, the book will supplement, but cannot replace, individual instruction, preferably by a dietitian.

B.

CLINICAL HEART DISEASE. By Samuel A. Levine, M.D., F.A.C.P. Philadelphia and London, 1951, W. B. Saunders Company. Fourth edition, illustrated, 556 pages. Price $7.75.

Dr. Levine has charmed a whole generation of physicians and students with his book of "fireside chats" on bedside cardiology. The preface to the first edition indicates that the book is designed for general practitioners. The present edition seems to be designed for physicians especially interested in internal medicine who have or will have some postgraduate education in electrocardiography. The first 300 pages consist of a series of informal lectures which combine factual information and clinical wisdom. Perhaps precious space is saved and distraction is avoided by omitting references to the names of some men who have contributed significant items of knowledge. Yet this anonymity of the older and the newer great developments makes them seem less real, less subject to further change than if they had some tangibly human indentification.

In the preface to this edition, we learn that the chapter on electrocardiography has been entirely revised by Dr. Harold D. Levine in light of the "written and spoken word of Wilson, Ashman, and others." These 200 pages represent the equivalent of a monograph on electrocardiography. Some effective, original drawings and charts help to teach the "how" of the P,Q,R,S,T complexes, a rational basis for the interpretation of multiple limb and chest leads. The question as to whether ectopic rhythms are to be explained by the circus movement of Lewis or by the concept of a single focus recently supported by the work of Scherf and Prinzmetal and their associates is barely mentioned. Circus movement is suggested as the likely explanation of paroxysmal tachycardia and is described in only one sentence in the section on auricular flutter. As the arrhythmias remain an important part of the field of cardiology, the possible mechanisms of their origin merit more detailed discussion than appears in this book. The illustrations of electrocardiograms are well chosen. The variations in the appearance of the records reflect the changes in technique of recording and variable results of photography at different times in the past twenty-five years or more during which the records were collected. The variable degrees of reduction in the size of the illustrations might prove confusing to the novice. It is an advantage to the student if all the electrocardiographic illustrations are uniformly reduced. This book should continue to enjoy its well-deserved popularity.

H. S.

HEART DISEASE. By Emanuel Goldberger, M.D. Philadelphia, 1951, Lea & Febiger. Price $10.00.

As there have been published in recent years several textbooks covering the field of heart disease, it might seem that another would be superfluous. However, this volume fully justifies its existence and gives an excellent account of all types of cardiac lesions and the effect of different diseases on the heart. In view of the fact that most of the author's previous publications have been on electrocardiography, it might be thought that this phase would be stressed. This is not so, however. The book is essentially a clinical description balanced with an adequate presentation of the other diagnostic procedures utilized in the study of heart disease. If any aspect is stressed, it is the history and physical examination.

The opinions expressed by the author are conservative, and the most modern diagnostic methods and therapeutic procedures are described. In another edition it might be well for the author to include in the therapy of cardiovascular syphilis a discussion of the relative merits of penicillin and arsenicals. It seems that the arsenicals should be mentioned if for nothing else but to stress the caution that must be exercised in their use. At the end of each chapter there is an excellent bibliography which will be a great help in investigating any particular point on which a reader desires more detailed information than can be given in a textbook. The book can be recommended to the specialist and practitioner as one covering all aspects of the subject in a most accurate and satisfactory manner.

C.

THE PHYSIOLOGY AND PATHOLOGY OF HEMOSTASIS. By Armand J. Quick, Ph.D., M.D., Professor of Biochemistry, Marquette University School of Medicine. Philadelphia, 1951, Lea & Febiger, 188 pages, 18 illustrations, 21 tables. Price $4.00.

In recent years tremendous strides have been made in the study of the coagulation of blood and in the broad subject of hemostasis. This monograph presents these advances in a succinct and practical manner. The author, who has contributed so extensively to hematologic progress, is able to correlate clearly the vast amount of data available and to supplant the older, outworn theories with a newer, well-supported hypothesis of blood coagulation, an hypothesis which provides a practical scheme for the diagnosis and treatment of hemorrhagic diseases and contributes to the understanding of thromboembolism.

Starting with an excellent historical review of the development of concepts of hemostasis, he points out that effective stanching of blood is achieved only by an orderly correlation of three forces: vascular contraction after injury, coagulation of the blood, and platelets. The coagulation mechanism, particularly the group of reactions that bring about the formation of thrombin, plays a vital role in this hemostatic process. The author's concept of this mechanism correlates

the known facts concerning the prothrombin complex, the thromboplastin-prothrombin reaction, and the thrombinogenic cycle. Thrombin, in addition to clotting fibrinogen, labilizes platelets, thereby setting into play a chain reaction, since the agent liberated activates thromboplastinogen. Moreover, the disintegrating platelets supply a vasoconstrictor principle, thus linking the coagulation reaction with the vascular factor in hemostasis. Other factors contributing to stanching are a primary vascular contraction, probably reflex in nature, and the stickiness of compressed and injured endothelial lining. The fibrin clot functions primarily as a reservoir of entrapped platelets and an adsorbent of thrombin, localizing thrombosis and maintaining sustained hemostasis by a continuous liberation of the vascoconstrictor principle.

A classification of hemorrhagic diseases is proposed in which there is a primary division into (1) bleeding diseases due to vascular defect (angiostaxis) and (2) bleeding diseases due to factors in the blood (hematostaxis). The latter group is subdivided into the hypothromboplastinemias, the hypoprothrombinemias, and the hypofibrinogenemias. An excellent discussion is provided of the mechanisms involved in the various important hemorrhagic diseases, the diagnostic features of each are outlined, and therapeutic measures based upon sound analysis of existing information are summarized. From a diagnostic standpoint, only three tests are needed in the majority of instances: (1) the bleeding time, (2) the prothrombin time, and (3) the prothrombin consumption determination.

An excellent chapter is devoted to the subject of venous thrombosis. Consideration is given to the various factors involved in intravascular clotting, and considerable emphasis is placed upon the importance of clot retraction in the origin of the type of thrombi likely to result in embolic accidents. A brief discussion of therapeutic measures is presented.

Inasmuch as most of the important advances in hemostasis have resulted from laboratory studies, the second one-half of the book is devoted to a presentation of those laboratory methods essential for the study of bleeding diseases and for the control of anticoagulant therapy. Twenty-one tests are described under the headings of definition, principle, required apparatus, reagents, procedure, application, and interpretation.

This volume is an extremely valuable contribution and is highly recommended for stimulating reading and for reference use to clinicians and laboratory workers alike.

D.

Notice

Research Grants and Fellowships

To Be Made Available in 1952 by the Life Insurance Medical Research Fund

Applications for 1952 grants in aid of research on cardiovascular problems will be received by the Life Insurance Medical Research Fund up to Nov. 15, 1951. Support is available for physiological, biochemical, and other basic research which bears on cardiovascular problems, as well as for clinical investigation in this field. Preference is given to fundamental research. It is expected that about $600,000 will be awarded in these grants.

Applications for postdoctoral fellowships for training in research in 1952-1953 will also be received by this Fund up to Nov. 1, 1951. Preference will be given to candidates who wish to work in the broad field of cardiovascular function or disease and to candidates who wish to work in institutions other than those in which they have obtained most of their experience. A doctor's degree (M.D. or Ph.D.) or the equivalent is required. The annual stipend varies, as a rule being between $3,000 and $4,000, with larger amounts in special cases. Approximately fifteen new postdoctoral fellowships will be available.

New grants and fellowships will become available on July 1, 1952.

A number of predoctoral fellowships for basic training in research will also be awarded. Details are available on request.

Further information and application blanks may be secured from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103rd St., New York 29, N. Y.

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